PHARMACOTHERAPY

PREPARATORY REVIEW AND RECERTIFICATION COURSE

VOL 2 | 2023 ACCP UPDATES IN THERAPEUTICS®

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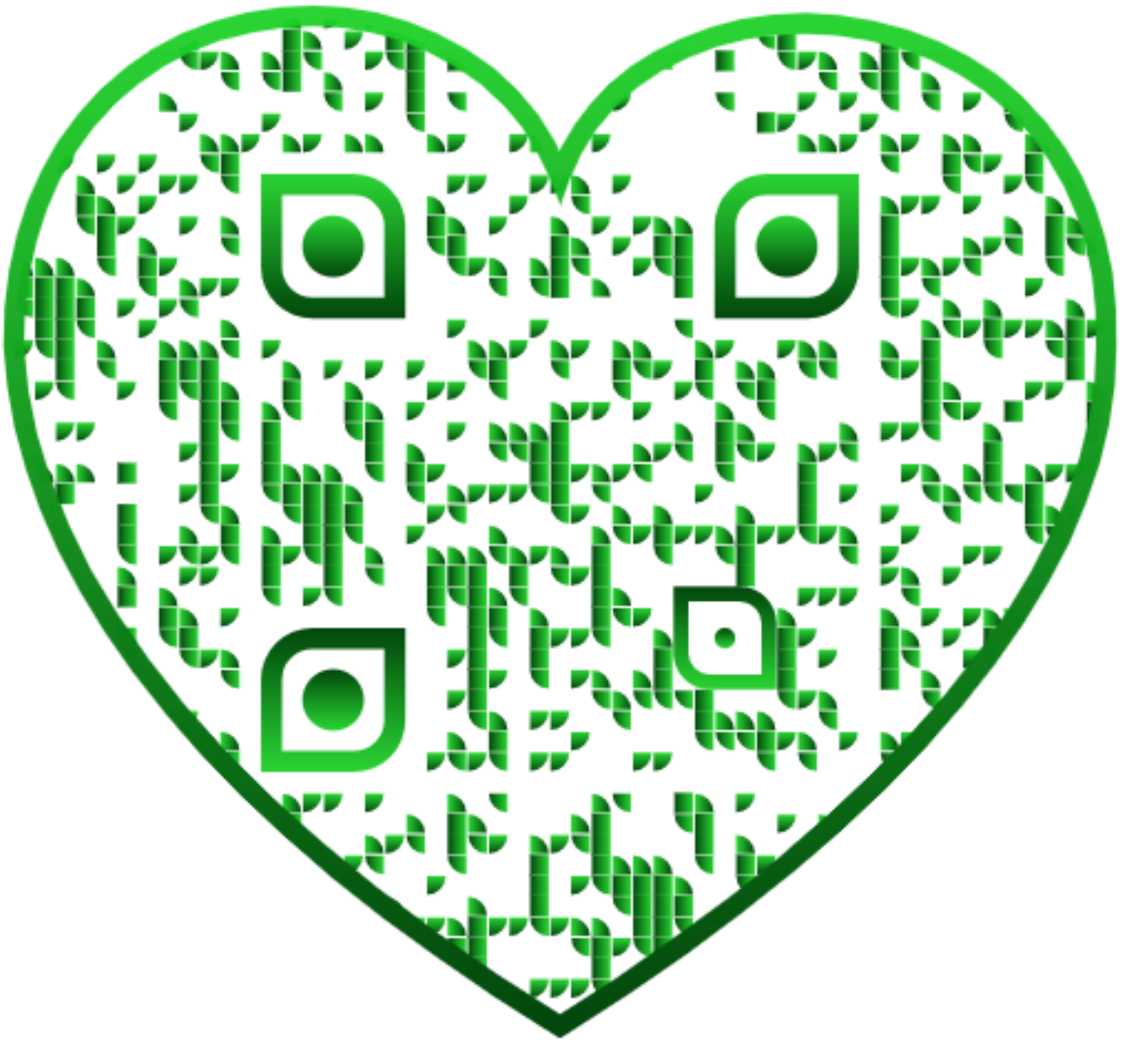

American College of Clinical Pharmacy

Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

American College of Clinical Pharmacy

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2023 Edition
Volume 2

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Note: The authors and publisher of the Pharmacotherapy Preparatory Review and Recertification Course recognize that the development of this material offers many opportunities for error. Despite our very best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check other published sources to be certain that recommended dosages and contraindications are in agreement with those listed in this book. This is especially important in new, infrequently used, or highly toxic drugs.

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Continuing Pharmacy Education:
The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers for the Pharmacotherapy Preparatory Review and Recertification Home Study Course, 2023 edition, are as follows: Acute Care in Cardiology, Chronic Care in Cardiology, and Anticoagulation, Activity No. 0217-0000-23-016-H01-P, 4.25 contact hours; Infectious Diseases I, Infectious Diseases II, Critical Care, and Fluids, Electrolytes, and Nutrition, Activity No. 0217-0000-23-017-H01-P, 4.25 contact hours; General Psychiatry, Neurology, and Sexual and Reproductive Health, Activity No. 0217-0000-23-018-H01-P, 4.0 contact hours; Healthcare Systems and Population Health, Oncology Supportive Care, Pharmacokinetics: A Refresher, and Gastrointestinal Disorders, Activity No. 0217-0000-23-019-H01-P, 4.25 contact hours; Endocrine and Metabolic Disorders, Nephrology, Geriatrics, and Pulmonary Disorders and Adult Immunizations, Activity No. 0217-0000-23-020-H01-P, 4.75 contact hours; Pediatrics, Biostatistics: A Refresher, Study Designs: Fundamentals and Interpretation, and Drug Information and Communication Strategies in Pharmacy, Activity No. 0217-0000-23-021-H01-P, 4.75 contact hours. All Pharmacotherapy Preparatory Review and Recertification Course sessions are application-based activities.

To earn continuing pharmacy education credit for the home-study version of the 2023 Pharmacotherapy Preparatory Review and Recertification Course, you must review all content and complete the attestation statements and course evaluations by May 3, 2026. Statements of continuing pharmacy education credit will be available at CPE Monitor within 2–3 business days after completion of this activity.

Board Certified Pharmacotherapy Specialist (BCPS) Recertification Credit
The Pharmacotherapy Preparatory Review and Recertification Course is part of a Board of Pharmacy Specialties (BPS)-approved professional development program for BCPS recertification credit. To be eligible to earn the 26.25 contact hours of pharmacotherapy recertification credit for the Pharmacotherapy Preparatory Review and Recertification Course, you must purchase and successfully submit the completed web-based posttest(s) by 11:59 p.m. (CDT) on May 3, 2024. To learn more about the Board of Pharmacy Specialties (BPS) specialty exams, please visit their website: www.bpsweb.org.

The American College of Clinical Pharmacy (ACCP) has compiled the materials in this course book for pharmacists to use in preparing for the Board of Pharmacy Specialties (BPS) Pharmacotherapy Specialty certification examination. There is no intent or assurance that all of the knowledge on the examination will be covered in the ACCP process. Although ACCP does use the BPS Content Outline in creating the material for this course, ACCP does not know the specific content of any particular BPS examination. BPS guidelines prohibit any overlap of individuals writing the examination and developing preparatory materials. To maintain its strict, independent standards for certification, BPS does NOT endorse or provide review information, preparatory courses, or study guides for Board Certification Examinations.

Program Goals and Target Audience

The Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Pharmacotherapy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in pharmacotherapy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

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American College of Clinical Pharmacy

Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

Healthcare Systems and Population Health

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Healthcare Systems and Population Health

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Learning Objectives

1. Choose the quality improvement tools, surveillance activities, and technology support needed by an interprofessional team when evaluating medical errors, adverse drug events, appropriateness of treatment, and new services for potential failures.
2. Recommend resources to use when planning immunizations and screenings for individuals and populations.
3. Evaluate an emergency preparedness plan for an organization, noting the basic components.
4. Select evidence-based and best practices for instruction for didactic presentations, experiential learning, and patient education.

Abbreviations in This Chapter

ADE	Adverse drug event
ADR	Adverse drug reaction
AHRQ	Agency for Healthcare Research and Quality
APhA	American Pharmacists Association
P&T	Pharmacy and therapeutics (committee)
QI	Quality improvement
TJC	The Joint Commission
USPSTF	U.S. Preventive Services Task Force

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. The pharmacy and therapeutics (P&T) committee at your hospital wants to establish a new program to evaluate opioid use and develop interventions to reduce inappropriate use. Which quality improvement (QI) tool would be best to use?
   A. Pareto chart.
   B. Plan-do-study-act.
   C. Driver diagram.
   D. Flowchart.

2. A new physician orienting to medication use at your hospital asks why there is a formulary. She wants the ability to prescribe any medication marketed in the United States for her patients. Which is the best response?
   A. Formularies increase standardization, thereby increasing patient safety.
   B. Sticking to formulary medications will help in monitoring adverse drug reactions (ADRs).
   C. Formularies improve the pharmacy's ability to lend medications to other hospitals.
   D. Physician autonomy does not include the ability to prescribe any medication.

3. A geriatric clinic hires a pharmacist to develop and manage its immunization services. Which resource is best to use for writing policies on procuring, storing, and administering vaccines in the clinic?
   A. U.S. Preventive Services Task Force (USPSTF).
   B. American Pharmacists Association (APhA) Immunization Center.
   C. Infectious Diseases Society of America.
   D. The Joint Commission (TJC).

4. A community pharmacy wants to expand services to provide point-of-care testing for recommended adult screenings. Which would provide the most guidance for evidence-based recommended screening in this population?
   A. WHO.
   B. Agency for Healthcare Research and Quality (AHRQ).
   C. USPSTF.
   D. State board of pharmacy.

5. The pharmacist assigned to a Gulf Coast hospital's emergency preparedness committee is asked which type of disaster would be most important to include in its annual emergency drills. Which is the best answer?
   A. Hurricane/flood response.
   B. Wildfire disaster.
   C. Terrorist attack.
   D. Asteroid strike.

6. A pharmacist is creating a continuing education program on new medications for other pharmacists. Evidence-based teaching suggests which as the most important first step in developing the program?
   A. Poll pharmacists to identify new drugs they are dispensing.
   B. Write self-assessment questions to use before and after the presentation.
   C. Prepare a detailed lecture outline.
   D. Develop learning objectives for participants.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1.4: Knowledge statements 1.4.1 – 1.4.3
    b. Task 1.5: Knowledge statements 1.5.1, 1.5.2
2. Domain 2: Application of Evidence to Practice and Education
    a. Task 2.3: Knowledge statements 2.3.2, 2.3.4, 2.3.5
3. Domain 3: Healthcare Systems and Population Health
    a. Task 3.1: Knowledge statements 3.1.1 – 3.1.3, 3.1.5
    b. Task 3.2: Knowledge statements 3.2.1, 3.2.4
    c. Task 3.3: Knowledge statements 3.3.1 – 3.3.4
    d. Task 3.4: Knowledge statements 3.4.1 – 3.4.4

I. INTRODUCTION

A. Review Aspects of Healthcare Systems and Population Health

B. Describe Evidence-Based Practices for Teaching and Patient Education

II. QUALITY IMPROVEMENT (QI)

A. Quality Assurance (inspection of processes)
   1. Punishing individuals for errors
   2. Myth that perfection was required of health care providers (and was attainable)
   3. Quality control, as in manufacturing

B. Paradigm Shift in QI
   1. Publications by the Institute of Medicine (now the National Science Academy)
      a. "*To Err Is Human: Building a Safer Health System*" and "*Crossing the Quality Chasm: A New Health System for the 21st Century*"
      b. Themes to improve quality
         i. Human factors engineering
         ii. Health information infrastructure
         iii. Meaningful use of health information technology
         iv. Improved access to information
         v. Protection of health information
      c. Call for change in health care delivery to improve health care outcomes by revision of patient care processes and the patient–provider relationship

C. Principles of QI
   1. Focus on the system and the team as large contributors to medical errors
   2. Recognize the fallibility of humans in providing patient care
   3. Evaluate errors as an opportunity to learn ways to improve the system
   4. System should have checks and balances that support the individual so that errors are unlikely.
   5. Errors are reviewed by peers to identify contributors to their occurrence so that changes can be adopted to prevent a future error.

D. W. Edwards Deming
   1. Champion for QI
   2. 14 points written for manufacturing QI that provide a foundation for looking at controlling the variability in processes in order to achieve improvement (Box 1)
   3. Provide guidance for health care organization QI

E. Application to Healthcare
   1. When first proposed, many individuals doubted they could be applied in the healthcare industry.
      a. Variability of the human condition
      b. Unique individual issues
   2. Have proven useful in reducing variability and involving the workforce in improvement of processes

F. When an Organization Adopts a QI Mindset, then Upper-level Management will
   1. Establish the importance of QI
   2. Educate the organization's leadership
   3. Set clear roles and responsibilities for individuals on the team

G. Many healthcare organizations have implemented the Model for Improvement.
   1. Involves testing changes through the plan-do-study-act cycle where improvement changes can be evaluated for effectiveness and issues before being adopted by the entire organization
   2. Other popular frameworks are Six Sigma, Lean, and Lean Six Sigma, which focus on removing waste, duplication, and non–value-added steps in a process.

Box 1. Deming's 14 Points for Manufacturing Quality Improvement

1. "Create constancy of purpose toward improvement." Think long-term planning, not short-term reaction
2. "Adopt the new philosophy." Management as well as the workforce should actually adopt this philosophy
3. "Cease dependence on inspection." If variation is reduced, there is no need for inspection because defects (errors) will be reduced or eliminated
4. "Move toward a single supplier for any one item." Having multiple suppliers means increased variation
5. "Improve constantly and forever." Focus on continuous quality improvement
6. "Institute training on the job." Lack of training leads to variation among workers
7. "Institute leadership." This draws the distinction between leadership, which focuses on vision and models, and supervision, which focuses on meeting specific deliverables
8. "Drive out fear." Management through fear is counterproductive and prevents workers from acting in the organization's best interests
9. "Break down barriers between departments." Eliminate silos. All departments are interdependent and become each other's customers in producing outputs
10. "Eliminate slogans." It is not people who make most mistakes – it is the process in which they are working
11. "Eliminate management by objectives." Production targets encourage shortcuts and the delivery of poor-quality goods
12. "Remove barriers to pride of workmanship." This leads to increased worker satisfaction
13. "Institute education and self-improvement"
14. "The transformation is everyone's job"

H. Individuals and teams require training to meet challenges and overcome barriers.
   1. QI tenets, skills, and tools
   2. Personal attributes needed include enthusiasm, curiosity, and collaboration.
   3. Training resource: Institute for Healthcare Improvement
   4. Essential tools (Table 1)

Table 1. Essential Tools for QI

Tool	Use
Cause-and-effect diagram (i.e., Ishikawa or fishbone diagram)	Graphically displays relationships of many causes contributing to an outcome
Driver diagram	Visual display of what primary and secondary items contribute to achievement of an aim
Failure Mode and Effects Analysis (FMEA)	Predicts where, how, and to what extent a system failure could occur so that improvements can be devised to prevent the failure
Flowchart, Process mapping	Visual map of the steps in a process
Histogram	Displays continuous data over time to reveal variation
Pareto chart (80/20 rule)	Bar chart of contributing factors arranged from largest to smallest
Plan-do-study-act cycle	Documents testing a change
Project planning	Systematically plans the changes to be tested
Run chart (control chart)	Graphs data over time (run chart) and, with the addition of upper and lower control limits (control chart), helps distinguish causes of variation
Scatter diagram	Helps identify cause-and-effect relationships between two variables

III. TECHNOLOGY

A. Dispensing was the initial focus for QI supported by technology.

B. Accuracy and Timeliness of dispensing is improved when barcode dispensing, automated dispensing, and other robotic supports are implemented.

C. These dispensing systems also allow improved management of inventory, which reduces cost.

D. Evolution of the electronic health or electronic medical record added other patient safety features.

E. Computerized Order Entry and Electronic Medical Records
   1. Dispensing
   2. Administration systems, helping to ensure the right drug is administered to the right patient at the right time
   3. Intelligent infusion devices
   4. Incorporating clinical decision support systems to help prescribers select the right drug at the right dose and help the organization meet important quality indicators
   5. Implementation of QI programs and projects with ease of data collection
   6. Surveillance of antibiotic prescribing, opioid prescribing, and adverse drug events (ADEs)
      a. Timely when reports are generated by electronic health records
      b. Allow implementation opportunities for intervention in real time to increase patient safety

F. Automatic Capture and Reporting of Information
   1. Identify patients who require review and intervention, such as laboratory values and dosing issues
   2. Documentation and management tools
   3. Reporting pharmacy/pharmacist metrics and patient outcomes data

G. Telepharmacy: Improves access, outcomes, and patient safety

H. Online Access to Medical Records
   1. Exceeded the Healthy People 2030 goal
   2. Patients can better track and manage their health care with this access

IV. QUALITY MEDICATION USE IN HEALTHCARE SYSTEMS

A. Formulary Systems
   1. One of the first quality initiatives used by healthcare systems
   2. A formulary is defined as a continually updated list of medications.
   3. Standardizing the list of medications for use
      a. Reduces variability in practices
      b. Improves efficiencies
   4. TJC standard on medication management requires hospitals to develop and approve criteria for identifying formulary medications.
   5. Criteria include indications for use, effectiveness considerations, drug interactions, ADEs, potential for errors and sentinel events, other risks, and costs.
   6. The P&T committee is usually delegated responsibility for implementing this standard and any associated policies and procedures. Formulary management tools used by the P&T committee usually include:
      a. Preference for generic drugs
      b. Restricted/prior authorization for use of specific drugs
      c. Policy/procedure to obtain non-formulary agents
      d. Therapeutic interchange according to protocol
      e. Medication use criteria

B. Medication Use Evaluations
   1. Evaluation of medication use processes and outcomes
   2. Goal is to improve safety, effectiveness, and costs.
   3. May evaluate any or all steps of medication use process, including prescribing, dispensing, administration, monitoring, and system management
   4. Medication use evaluations are part of an interprofessional QI program.
   5. Responsibility of the P&T committee

C. Surveillance in the Healthcare System
   1. Antibiotic stewardship
      a. Required for hospitals, critical access hospitals, and nursing care centers by TJC as of 2017
      b. The standard addresses concerns with antibiotic resistance and the reported unnecessary use of antimicrobials (up to 50% of antibiotic prescriptions).
      c. CDC Core Elements of Hospital Antibiotic Stewardship Programs

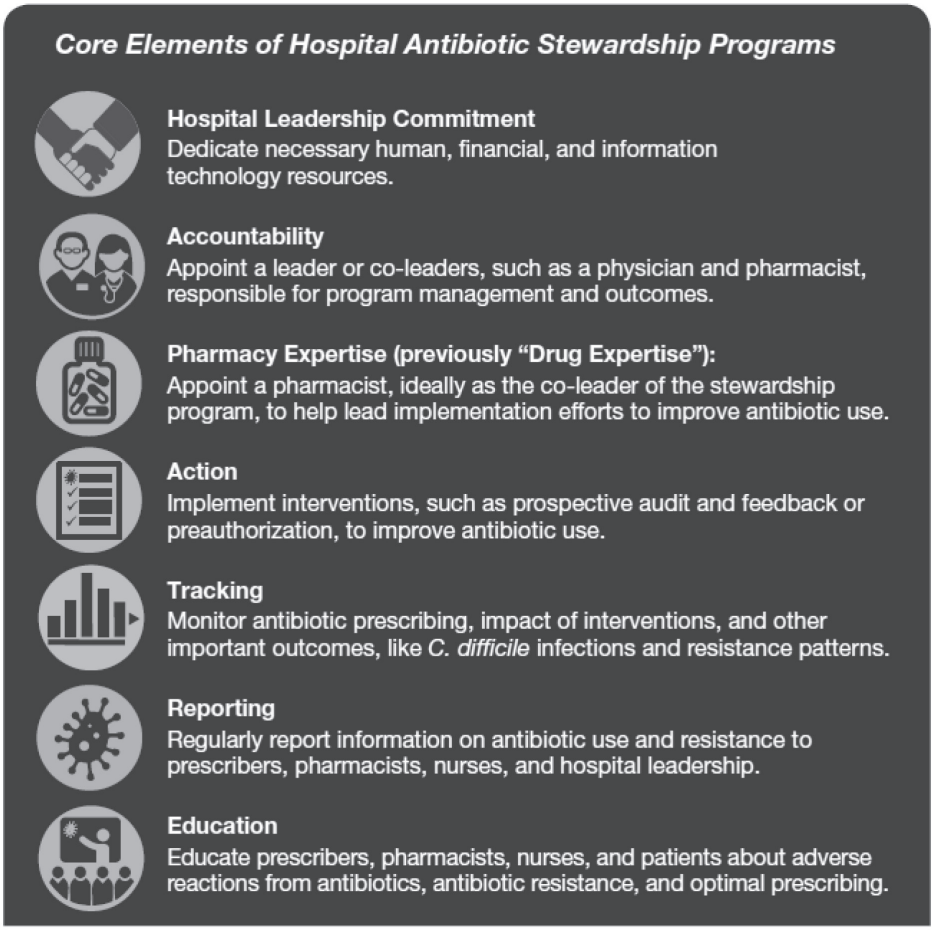
Core Elements of Hospital Antibiotic Stewardship Programs
Hospital Leadership Commitment
Dedicate necessary human, financial, and information technology resources.
Accountability
Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes.
Pharmacy Expertise (previously "Drug Expertise"):
Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use.
Action
Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.
Tracking
Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like C. difficile infections and resistance patterns.
Reporting
Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.
Education
Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

Figure 1. CDC Core Elements of Hospital Antibiotic Stewardship Programs.

Source: CDC. Core Elements of Hospital Stewardship Programs. US Department of Health and Human Services. CDC, 2019. Available at https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf. CDC Disclaimer: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. This material is available on the agency website for no charge.

d. Resources found on the Infectious Diseases Society of America website:
    i. Describe the purpose of these programs to be in compliance with evidence-based guidelines for antimicrobial prescribing
    ii. Also name the personnel required to include a pharmacist trained in infectious diseases together with a physician (preference for infectious disease education/training), a microbiologist, and an infection control expert
e. Required surveillance monitoring includes:
    i. Identifying patients with redundant antimicrobial coverage
    ii. Overall antimicrobial use on a quarterly basis
    iii. Daily review of antibiotics from a proposed list of restricted-use agents
    iv. Daily activities should also include escalation and de-escalation of pathogen coverage, intravenous-to-oral conversions, pharmacokinetic monitoring, and renal dose adjustments.

2. ADR reporting
    a. ADRs, ADEs, and medication errors are related and overlap (Table 2).
    b. ADR reporting developed as a means of postmarketing surveillance for the FDA.
    c. Required reporting by manufacturers; voluntary for clinicians, patients
    d. All ADRs are ADEs, but the ADE definition includes overdose. Some also include omission or underdose of an indicated drug as ADEs.
    e. Medication errors initially focused on deviations in dispensing and administering from the prescribed order/prescription. Now also include errors in prescribing and monitoring
        i. May result in patient harm
        ii. Useful to monitor for system defects
        iii. "Near misses" may also be reported where error was caught before it reached the patient.
    f. ADEs came to the forefront in the United States when the Institute of Medicine published *"To Err Is Human*."
        i. This report highlighted that up to 50% of ADEs are the result of unsafe medication use.
        ii. Estimated costs associated with ADEs include 350,000 hospitalizations and 1 million ED visits annually.
    g. Newer systematic review of ADR studies indicates 16% of hospitalized older adults experience an ADR and more than 50% of these ADRs were judged preventable
    h. Technology allows for reporting and analysis of ADRs in large databases to identify areas for improvement
    i. Hospitals and healthcare systems must have policies and procedures for reporting and evaluating ADEs.
    j. Tools and resources are available to assess, prevent, and resolve ADEs.
        i. Naranjo algorithm includes 10 questions to standardize assessment of the probability that a drug caused a clinical event.
        ii. Root cause analysis involves reconstruction of the occurrence of an error and multidisciplinary analysis of how and why it happened.

Table 2. ADRs, ADEs, and Medication Errors

Term	Definition	Tools/Notes
Adverse drug reaction (*ADR*)	Any response to a drug at doses normally used in humans	Reported through MedWatch (drugs) and VAERS (vaccines); Naranjo algorithm and WHO Uppsala Monitoring Centre Scale assess causality
Adverse drug event (*ADE*)	An injury resulting from a medical intervention related to a drug	National Action Plan for ADE Prevention goals to identify significant ADEs and align efforts to reduce ADEs
Medication error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer	Most do not lead to significant patient harm Those that do are also classified as ADRs or ADEs

3. Pain assessment and management
    a. TJC requires surveillance activities.
    b. Opioid stewardship programs are an effective way to ensure a facility is meeting these standards.
    c. In states where prescription drug monitoring programs must be consulted before prescribing opioids, accreditation surveyors will ensure compliance with state law.

V. POPULATION HEALTH

A. Public health is the science of preventing disease, prolonging life, and promoting wellness in a population through organized efforts by local, state, and national governments that are accountable to the community.
   1. Links science with actions for a population
   2. Involves research, education and policy to achieve improved outcomes
   3. Pharmacists are often overlooked as contributors to population health.

B. Population health is also focused on the health of a population rather than each individual person.
   1. Includes social and economic factors that contribute to a population's health
   2. Efforts may be government-run but are also run by hospitals or volunteer organizations.

C. Population health management refers to the steps taken by healthcare organizations to improve the health outcomes of a defined group of individuals.

D. Population Health Management Cornerstones
   1. Disease surveillance
   2. Disease prevention:
      a. Immunizations
      b. Health screenings
   3. Preventive medicine
   4. Emergency preparedness

E. Disease Surveillance
   1. First established in the context of public health before being applied to medication use within a health system
   2. Ongoing systematic collection, analysis, and interpretation of health-related data essential to planning, implementing, and evaluating public health practice. Timely dissemination of the data, analysis, and interpretation is needed to prompt action by public health professionals, government leaders, and the public.
   3. The recent COVID-19 pandemic is an example of active disease surveillance that changed practice rapidly as new information was obtained.
   4. Pharmacists became important sources of information as recommended vaccinations and monoclonal antibody administration were provided in local pharmacies and hospitals.
   5. Pharmacists reported informally on the use of non-approved therapies (i.e., hydroxychloroquine, ivermectin).

F. Disease Prevention: Immunizations
   1. Immunizations recommended by the Advisory Committee on Immunization Practices (ACIP) to the CDC
   2. Immunization schedules published by the CDC annually after review
   3. Schedules are divided by age:
      a. Children (birth to age 18)
      b. Adults 19 years and older
      c. Recommendations for travelers and pregnant women are available on the CDC website.
      d. Includes medical conditions, comorbidities, special situations, contraindications, and precautions to guide health care provider recommendations

4. U.S. pharmacists can vaccinate patients:
    a. Laws vary from state to state with respect to regulations on patient ages, vaccines, and need for a prescription.
    b. APhA maintains vital information on storage and administration of vaccines for pharmacists providing vaccinations on its immunization center website.
    c. Immunization Action Coalition (www.immunize.org) provides information for health care providers, the public, and immunization coalitions.

G. Disease Prevention: Health Screenings
1. Health screenings recommended by the USPSTF
    a. An independent, volunteer panel of experts
    b. Develops evidence-based recommendations
    c. Focuses on clinical preventive services apart from immunizations
2. USPSTF website recommendations are categorized for patients by age, sex, pregnancy status, grade, category of disease/condition, and type of service.
3. Thirteen recommended items involve counseling, 10 are for preventive medications, and 29 are for screening. Screening may require laboratory procedures or questionnaires.

H. Preventive Medicine
1. May be targeted for one patient at a time or focus on populations at any level:
    a. Insured lives,
    b. Employees of a company, or
    c. Members of a community
2. State- and national-level disease prevention may involve laws and regulations of businesses, manufacturers, health professionals, and highways.
3. States, nations, and international organizations offer voluntary opportunities for disease prevention.
4. Disease prevention activities are categorized as primary, secondary, or tertiary (Table 3). Pharmacists are involved in each of these areas with providing medications and patient counseling and reporting trends to public health entities.

Table 3. Types of Disease Prevention

Level of Disease Prevention	Patient or Population Focus	Aim	Examples
Primary	General population or a specific at-risk population before the disease develops	Reduce exposure to risk factors and increase resistance to disease, thereby decreasing the number of cases	Immunizations Awareness campaigns
Secondary	Individuals exposed to or with early disease before morbidity occurs	Provide postexposure prophylaxis or early treatment before symptoms are identified	Antiviral agents for nursing home residents in an influenza outbreak Colonoscopy screening after age 45
Tertiary	Patients with disease causing morbidity	Reduce morbidity/mortality and return individual to better state of health	Support groups to improve adherence to diabetes treatment to prevent blindness Availability of antivirals for influenza to prevent pneumonia, hospitalization, and death

VI. EMERGENCY PREPAREDNESS

1. Disasters are sudden ecological phenomena of sufficient magnitude to require external assistance. Disasters may be natural or manmade, though most are natural.
    a. Natural disasters are forces of nature that are typically:
        i. Meteorological events caused by severe weather (most common)
        ii. Geologic events (earthquakes, volcanoes)
        iii. Celestial events (asteroids, solar flares)
        iv. Biological disasters (epidemics)
    b. Some disasters are manmade, though natural occurrences may also cause them:
        i. Radiation/chemical leaks, structural failures, or wildfires accidentally caused by humans
        ii. Technologic disasters, including power interruptions
        iii. Terrorism events have increased over the past 100 years.
2. Although no community can be prepared for every emergency, lack of planning results in lives lost.
3. Regularly scheduled hazard vulnerability analyses are performed by emergency preparedness professionals.
    a. State and local health departments
    b. Federal Emergency Management Agency (FEMA)
4. Identify a community's highest risk of disaster so that appropriate plans can be developed
    a. Trust for America's Health report "Ready or Not 2022" evaluated 10 indicators of emergency preparedness to rank states' level of preparedness.
    b. Most states have:
        i. Plans to expand healthcare capacity in an emergency
        ii. Public health and emergency management accreditations
        iii. Safe water
    c. Many are not prepared with
        i. Workforce resiliency including paid time off for illness or caring for family member, which was highlighted during the pandemic
        ii. Percentage of people vaccinated
        iii. Meeting patient safety standards
    d. Seventeen states have a high level of preparedness, which decreased from 2021. Thirteen states have a low level, and the rest rate in the middle tier.
    e. The WHO and the CDC agree that the United States is ill-prepared for many emergencies.
    f. Preparation requires
        i. Surge capacity anticipated for both personnel, space, and supplies
        ii. Supplies stockpiled with appropriate rotation to prevent expiration
        iii. A communication system with both primary and backup systems in case of primary system failure
        iv. Routine emergency drills to prepare employees and identify weaknesses in the response plan should occur routinely.
            (a) Simulated emergency response in the community
            (b) Tabletop drills to walk through steps in the plan
5. Well-trained pharmacists are essential when disasters occur and emergency plans are set in motion.
    a. Pharmacist roles most often involve procurement and distribution of medications, mass immunizations, and antibiotic dispensing.
    b. Support to their local community
    c. Mobilization with organizations like the American Red Cross, the National Pharmacy Response Team, and the Disaster Medical Assistance Team

VII. COMMUNICATION AND EDUCATION FOR PROVIDERS AND STAFF

A. Evidence Supporting Teaching, Precepting, and Learning
   1. Pharmacists need to be familiar with evidence that supports didactic and precepting strategies used in health professionals' education.
   2. To promote the best learning outcomes, teachers, preceptors, and administrators need to use evidence, not only in the content of what is taught or practiced but also in the process of teaching and learning (Box 2).

Box 2. Key Findings from Research That Can Inform Your Teaching and Precepting

1. Good teaching and precepting can promote better learning outcomes
2. A one-size-fits-all approach to teaching and learning does not work as well as multiple strategies
3. Millennials and younger generations are not as satisfied with traditional learning approaches, so their learning potential may be better achieved with more current strategies
   a. Their K–12 education has evolved to include more technology and newer approaches to teaching and learning
   b. Society's culture has evolved rapidly, whereas higher education has not
4. A student-centered model promotes better learning outcomes than a teacher-centered model
5. Instructional alignment can promote better learning outcomes
6. Active learning promotes better learning outcomes (e.g., retention, application) than passive learning (e.g., sitting in a lecture, possibly even with note taking)
7. Long lectures (even as short as 50 min) do not hold students' attention as well as short, punctuated lectures
8. Providing context and establishing relationships to practice and other content areas promotes better learning (e.g., vertical and horizontal integration)
9. Thoughtful repetition and scaffolding (i.e., going from simple to complex in a logical sequence) can promote better learning outcomes
10. Using readings with targeted questions or guides promotes better learning outcomes than assigned readings alone
11. Frequent assessment with feedback leads to better learning outcomes
12. Specific, objective, immediate feedback can improve learning outcomes
13. Critical thinking is best developed through modeling and demonstration
14. Writing improves critical thinking and learning retention and application

B. The main educational frameworks and guiding philosophies currently used in academic settings are learner-centered vs. teacher-centered teaching.

C. These are defined by their focus:
   1. What the student is learning
   2. How the student is learning
   3. The conditions under which the student is learning
   4. Whether the student is retaining or applying the learning
   5. How current learning prepares the student for future learning

D. Table 4 shows characteristics.

Table 4. Characteristics of Teacher- and Learner-Centered Education Models

Teaching Paradigm	Learning Paradigm
Stored knowledge model	Constructed knowledge model
Content centered	Ability centered
Instructor oriented	Student oriented
Didactic teaching	Active, experiential learning
Professional training	Professional education

Adapted from: Zlatic TD. Re-visioning Professional Education: An Orientation to Teaching. American College of Clinical Pharmacy, 2005.

E. When designing educational programming, Bloom's taxonomy is often incorporated as a way to design, assess, and diagnose student learning.

F. Educational psychologist Benjamin Bloom and colleagues originally defined levels of learning for three different learning domains (Figure 2).

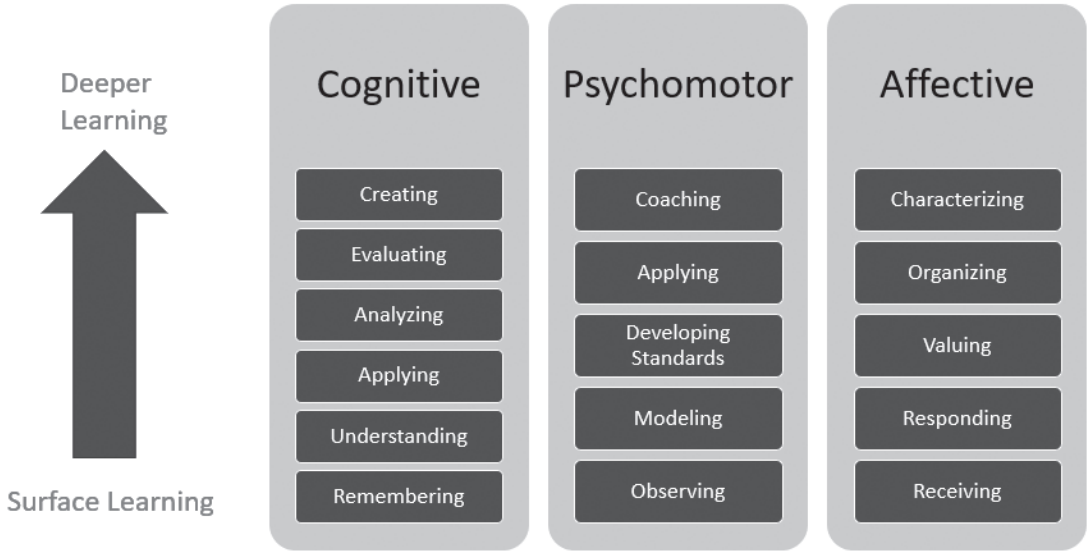

Figure 2. Bloom and Krathwohl's taxonomy of learning.
Information from: Krathwohl DR. A revision of Bloom's taxonomy: an overview. Theory Pract 2002;41:212-8.

G. The cognitive domain is the most widely used domain in education.

H. These taxonomies can be extremely helpful when creating objectives, instruction, and assessments (e.g., examination questions) designed to tap into specific levels of learning (Figure 3).

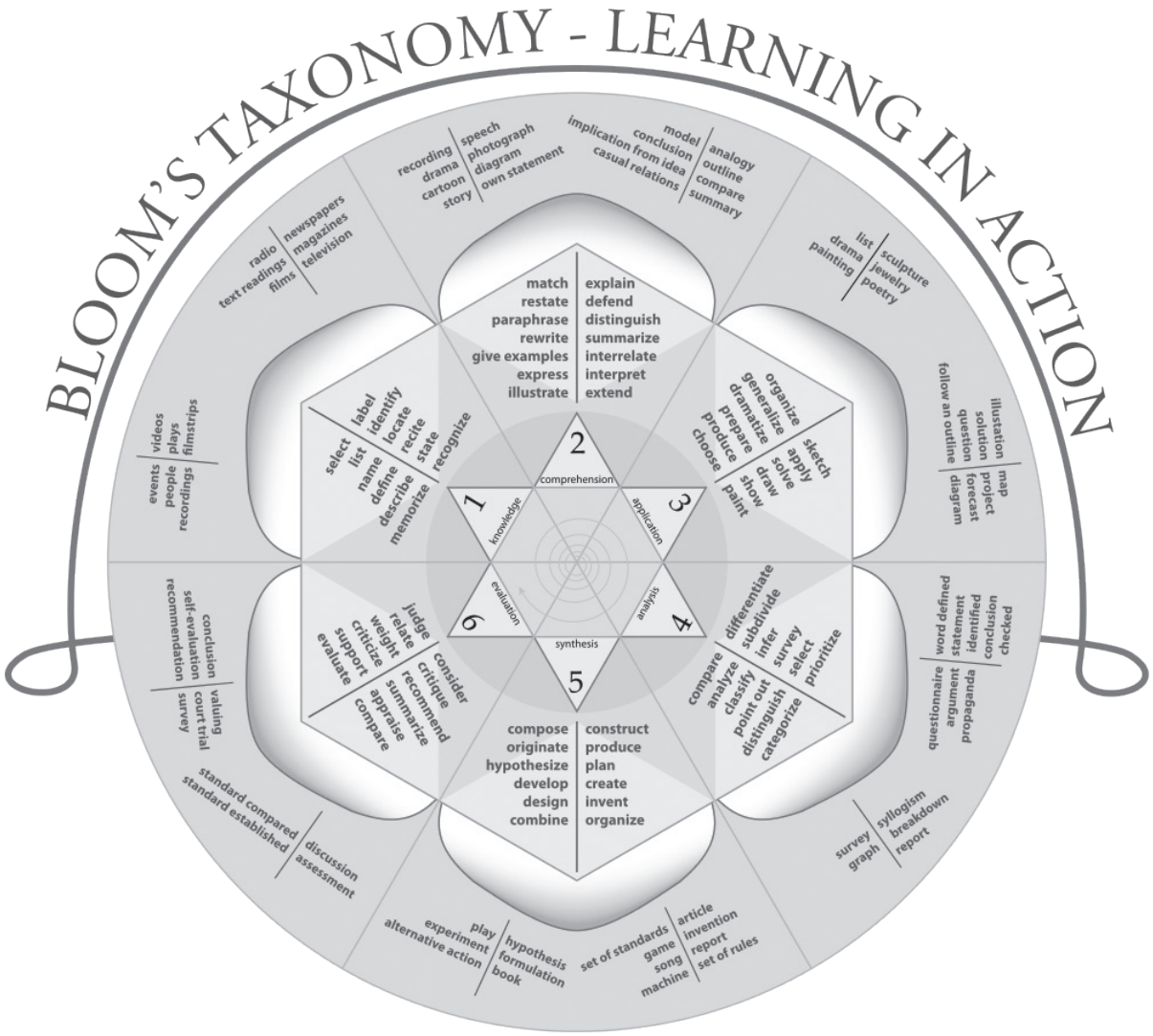
BLOOM'S TAXONOMY - LEARNING IN ACTION
1 knowledge
2 comprehension
3 application
4 analysis
5 synthesis
6 evaluation
match restate paraphrase rewrite give examples express illustrate
explain defend distinguish summarize interrelate interpret extend
label identify locate recite state recognize
select list name define describe memorize
organize generalize dramatize prepare produce choose
sketch apply solve draw show paint
differentiate subdivide infer survey select prioritize
compare analyze classify point out distinguish categorize
judge relate weight criticize support evaluate
consider critique recommend summarize appraise compare
compose originate hypothesize develop design combine
construct produce plan create invent organize
recording drama cartoon story
speech photograph diagram own statement
model conclusion implication from idea casual relations
analogy outline compare summary
list drama painting
sculpture jewelry poetry
illustration solution question follow an outline
map project forecast diagram
word defined statement identified conclusion checked
questionnaire argument propaganda
survey graph
syllogism breakdown report
set of standards game song machine
article invention report set of rules
play experiment alternative action
hypothesis formulation book
standard compared standard established
discussion assessment
conclusion self-evaluation recommendation
valuing court trial survey
radio text readings films
newspapers magazines television
events people recordings
videos plays filmstrips

Figure 3. Bloom's cognitive taxonomy (levels with numbers), associated verbs used for objectives (inner set of words), and potential instructional strategies to achieve those objectives (outer set of words).

Information from: Krathwohl DR. A revision of Bloom's taxonomy: an overview. Theory Pract 2002;41:212-8.

VIII. BARRIERS IN COMMUNICATION WITH PATIENTS AND CAREGIVERS

A. The most often-cited barriers in communicating with patients and caregivers include the poor health literacy of many patients and the lack of cultural competency exhibited by pharmacists and other clinicians.

B. Health Literacy
   1. Defined as how well a patient can obtain, process, and understand basic health information when needed to make a decision.

2. Ability to read is essential, but health-related materials require additional comprehension.
3. Low health literacy influences health disparities, reducing a patient's disease knowledge and health status and use of health services, including preventive care. It is associated with:
    i. Increased visits to hospital and emergency department
    ii. Decreased mammography
    iii. Decreased influenza vaccination
4. Medical expenditures and mortality are increased in groups with low health literacy.
5. Patients likely to have low health literacy include:
    a. Those living in poverty
    b. Those who do not speak English as a first language
    c. Adults older than 65
6. Access to information, health care services, and financial support has increasingly moved to an electronic format, which may add another barrier.
7. Healthy People 2030 added an objective to increase the health literacy of the population (in research status)
8. Five other specific objectives related to health literacy are:
    i. Increase proportion of health care providers who check patient understanding
    ii. Decrease proportion of health care providers with poor patient communication
    iii. Increase proportion of health care providers who involve patients in decision-making as much as they want
    iv. Increase proportion of people who say online medical record is easy to understand
    v. Increase proportion of adults with limited English proficiency who say their providers explain things clearly (in developmental stage)
9. Patients with low health literacy are adept at hiding it from providers. Many feel stigmatized if identified.
10. Controversy exists on whether to use surveys and questionnaires in clinical practice to identify patients with low health literacy because of the risk of shaming the individual.
    a. May use a one-question screening to help avoid stigma
    b. Example questions for one-question screening:
        i. Do you have trouble learning about their condition?
        ii. Do you feel confident filling out medical forms?
        iii. Do you rely on someone else to help read hospital materials?
11. Use of universal precautions is also a preferred method, which includes:
    a. Approach all patients as if they are at risk of not understanding health information
    b. Use a range of strategies for clear communication
    c. Confirm that patients understand what providers are saying
12. Health organizations should adopt policies and procedures that support productive interactions and improve outcomes in the communities they serve.

C. Cultural Competency
    1. Many definitions since the term was first used in the 1980s
        a. At first, the term addressed disparities in health outcomes and was used to improve clinicians' ability to care for patients of different racial and ethnic groups. Outcome disparities in many disease states were identified at that time, including myocardial infarction and breast cancer.
        b. Currently, diversity is often used in place of the term *cultural competency* to reflect the many facets of cultural and individual differences.
        c. The cultural competency of teams and organizations is part of the definition as policy changes provide necessary support to further enable clinicians to provide culturally appropriate care to patients.

   d. The Office of Minority Health has published standards for providing services that are culturally and linguistically appropriate.
      i. CLAS (culturally and linguistically appropriate services) includes three areas:
         (a) Culturally competent care
         (b) Language access services
         (c) Organizational supports for cultural competence
      ii. TJC and other accrediting bodies support organizational adoption of these elements.
2. Assessment tools are available for both individuals and organizations.
3. Understanding a clinician's own culture as well as the clinician's patient's culture enables incorporation of a shared perspective into the care plan.
4. Several models identify aspects of culture that usually influence individuals and their choices such as age, generation, nationality, race, color, sex, and religion. The ETHNIC(S) framework provides clinicians with a handy tool that can help honor a patient's culture during an encounter (Table 5).

Table 5. ETHNIC(S) Framework

Cultural Aspect	Direct Question or Statement to Be Asked or Stated (use the patient's phraseology)
Explanation	Why do you think you have this symptom/illness/condition?
Treatment	What have you tried for this symptom/illness/condition?
Healers	Have you sought any advice from folk healers?
Negotiation	Negotiate mutually acceptable options
Intervention	Agree on an intervention
Collaboration	Collaborate with patient, family, and healers
Spirituality	What role does your spiritual life play?

5. The platinum rule states: "Treat others as they would want to be treated." Keeping this in mind will help clinicians implement health literacy and cultural competency actions to overcome these types of barriers.

D. Teach-Back and Motivational Interviewing Modalities and Techniques
   1. Useful tools to ensure patients understand the information they have been given and can use any devices provided
   2. Useful for patients regardless of their level of health literacy
   3. Up to 80% of medical information received during an office visit is forgotten immediately, and 50% of what is retained is incorrect.
   4. Using the teach-back method promotes adherence, quality, and patient safety.
   5. Patients will be more accepting if the clinician:
      a. Is checking that things were explained clearly
      b. Asks patients to explain back in their own words what they heard or understand about what was said
   6. Motivational interviewing
      a. Evidence-based, patient-centered method of communicating that increases the likelihood of a desired change in behavior
      b. Motivational interviewing respects the patient's autonomy and builds the patient's self-efficacy.
      c. Autonomy can be supported using open-ended questions, setting an agenda, and asking permission before giving advice.
      d. Self-efficacy emerges when patients identify incremental changes they are willing to make.

7. Five main communication principles are at the core of motivational interviewing together with other micro skills, assumptions (Table 6). These are not natural to most pharmacists and should be practiced.

Table 6. Motivational Interviewing Principles

Principle	Application Example
Expressing empathy	Listen to a patient expressing disbelief, fear, or anger and validate that feeling "It sounds like you find this…"
Developing discrepancy	Create a thought-provoking discord for a resistant or ambivalent patient to begin to think about change. Sometimes repeating pros and cons stated by the patient or pointing out the disconnect between goals a patient has stated and their actions "So, on the one hand, you want to control your disease, but on the other hand, you don't like to take so many pills"
Supporting self-efficacy	Building a patient's confidence in the ability to make and sustain a change without overpraising. Focus on the behavior "It's great to see you were able to…"
Rolling with resistance	Avoid reacting negatively to a patient's resistant statements, and use them to explore the patient's reasons with open-ended questions "Tell me more about that"
Avoiding argumentation	Practice ignoring antagonistic statements made by the patient. Remind the patient that you are on their side and will be available whenever they want to make a change "May I tell you about my concerns for your health (if you continue to or if you don't start…)?"

IX. CONCLUSION

Healthcare systems and institutions have a responsibility to provide quality medication use for the patients they serve. This requires pharmacists to have knowledge and skills in use of QI, technology, formulary systems, medication use evaluations, and surveillance. Similar abilities are needed to meet the needs for population health, including disease surveillance, immunizations, preventive medicine, and emergency preparedness. Finally, to achieve optimal outcomes, excellent skills in teaching and learning are required to overcome barriers when communicating with other healthcare professionals, patients, and policy-makers.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
Answer B, plan-do-study-act, is correct because it will allow for exploring the problem without assuming what the problem is and will help in determining the best way to fix it. Plan-do-study-act provides an opportunity to design an intervention (plan), test it on a small scale (do), evaluate whether it worked (study), and then adopt, revise, or abandon it, as indicated (act). The other options – Pareto charts, driver diagrams, and flowcharts (Answers A, C and D) – help identify causes to a problem but do not help plan, test, or evaluate interventions for effectiveness, making them incorrect.

2. Answer: A
Answer A is correct because having a formulary reduces variability in practice, which improves efficiencies and safety. Formularies may help reduce ADEs but will not greatly assist in tracking or monitoring them (Answer B is incorrect). Formularies do not significantly affect lending medications (Answer C is incorrect). Discussing physician autonomy is more likely to inflame the situation than provide information to support formulary use so it is not the best answer (Answer D is incorrect).

3. Answer: B
The APhA Immunization Center supports pharmacists' involvement with immunizations, including information on procurement, storage, and administration, making Answer B correct. The Infectious Diseases Society of America is not focused on vaccines, but rather on setting guidelines for antimicrobial prophylaxis and treatment of vaccine-preventable diseases so they may improve patient quality of care through antimicrobial stewardship. (Answer C is incorrect). The USPSTF does not provide information regarding immunizations (Answer A is incorrect), and although TJC will survey a site to ensure it is following safe procurement, storage, and administration standards, it does not publish those standards (Answer D is incorrect).

4. Answer: C
The USPSTF provides information regarding recommended screenings, including those that involve point-of-care testing, making Answer C correct. The WHO provides guidance on the basis of the world stage, including countries in which point-of-care testing is cost-prohibitive (Answer A is incorrect). The board of pharmacy focuses on following state law to ensure patient safety (Answer D is incorrect). The AHRQ provides recommendations on best practices for healthcare organizations; however, it does not provide information on recommended screenings (Answer B is incorrect).

5. Answer: A
Natural disasters are the most common type of emergency; hence, annual drills should always include a type of disaster common for the area (Answer A is correct). Wildfires may be more common than hurricanes or floods in other regions of the country; however, they are not as common on the Gulf Coast (Answer B is incorrect). Terrorist attacks are increasing but are not the most common disasters, and asteroid strikes are extremely rare (Answers C and D are incorrect).

6. Answer: D
Developing the learning objectives is a way to begin with the end in mind, which is the best first step in developing a lecture (Answer D is correct). Polling pharmacists to identify new medications could skew the talk to miss new medications that would be important to cover (Answer A is incorrect). Preparing a detailed outline should follow the established learning objectives to ensure outcomes will be met by the lecture (Answer B is incorrect). Self-assessment questions are written after the learning outcomes have been created (Answer C is incorrect).

Oncology Supportive Care

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Oncology Supportive Care

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Learning Objectives

1. Recommend appropriate pharmacotherapy for managing common complications of cancer chemotherapy, including nausea and vomiting, myelosuppression and the appropriate use of growth factors, infection, anemia and fatigue, cardiotoxicity, and extravasation injury.
2. Recommend appropriate pharmacotherapy for managing cancer-related pain.
3. Recommend appropriate pharmacotherapy for managing oncologic emergencies, including hypercalcemia, tumor lysis syndrome, and spinal cord compression.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 50-year-old man is in the clinic to receive his third cycle of R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) for non-Hodgkin lymphoma. He is very anxious, with nausea and vomiting lasting for about 12 hours after his previous cycle of chemotherapy. The antiemetic regimen he received for his previous cycle of chemotherapy was granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy. Which regimen is most appropriate for the patient to receive on day 1 of the next cycle of chemotherapy?
   A. Granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy.
   B. Dolasetron 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.
   C. Netupitant/palonosetron 1 dose plus dexamethasone 1 dose plus lorazepam 1 dose administered 30 minutes before chemotherapy.
   D. Metoclopramide 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.

2. A 65-year-old man with metastatic non–small cell lung cancer is brought to the clinic by his family because he is lethargic and fatigued. Pertinent laboratory values include serum calcium concentration 12 mg/dL and albumin concentration 2 g/dL. Which therapy is best for this patient's lethargy and fatigue as the result of hypercalcemia of malignancy?
   A. Calcitonin 4 units/kg every 12 hours.
   B. Furosemide 20 mg orally.
   C. Dexamethasone 10 mg orally two times a day.
   D. Zoledronic acid 4 mg intravenously.

3. A 20-year-old man was recently given a diagnosis of acute myeloid leukemia. He has an elevated white blood cell count (WBC), and he will receive chemotherapy tomorrow. Which is the best prevention strategy for tumor lysis syndrome (TLS)?
   A. Hydration with 5% dextrose (D_5W), 1 L before chemotherapy, plus allopurinol 300 mg/day.
   B. Hydration with D_5W, 100 mL/hour starting at least 24 hours before chemotherapy, plus allopurinol 300 mg/day.
   C. Hydration with normal saline 250 mL/hour starting at least 24 hours before chemotherapy plus allopurinol 300 mg/day.
   D. Hydration with normal saline 100 mL/hour starting at least 24 hours before chemotherapy plus sodium bicarbonate 500 mg orally every 6 hours.

4. An 18-year-old man is about to begin chemotherapy with curative intent for acute lymphoblastic leukemia. On today's complete blood cell count (CBC), his hemoglobin (Hgb) is 7 g/dL, and he is experiencing fatigue. Which is the best treatment recommendation?
   A. Initiate epoetin.
   B. Administer transfusion of packed red blood cells (RBCs).
   C. Delay chemotherapy treatment until Hgb recovers.
   D. Reduce chemotherapy dosages to prevent further decreases in Hgb.

Questions 5–7 pertain to the following case.
A patient received her fourth cycle of chemotherapy with paclitaxel/carboplatin for ovarian cancer 12 days ago. She reports to the clinic this morning with a temperature of 103°F. Her CBC is WBC 500 cells/mm^3, segmented neutrophils 55%, band neutrophils 5%, basophils 15%, eosinophils 5%, monocytes 15%, and platelet count 99,000 cells/mm^3. She denies any signs or symptoms of infection. Her blood pressure is 115/60 mm Hg, heart rate is 80 beats/minute, and respiratory rate is 15 breaths/minute.

5. Which best represents the patient's absolute neutrophil count (ANC)?
   A. 275 cells/mm^3.
   B. 300 cells/mm^3.
   C. 25 cells/mm^3.
   D. 500 cells/mm^3.

6. Which is the best course of action for this patient?
   A. Admit her to the hospital for parenteral antibiotic drugs.
   B. Treat her as an outpatient with antibiotic drugs.
   C. Initiate a colony-stimulating factor (CSF).
   D. Discontinue chemotherapy.

7. Which statement about this patient is most accurate?
   A. Given her monocyte count, her neutropenia is expected to last for another week.
   B. This is a nadir neutrophil count, and neutrophils would be expected to start increasing soon.
   C. The elevated absolute eosinophil count indicates an allergic reaction to carboplatin.
   D. It is unusual for the ANC to be this low in the setting of an elevated platelet count.

8. A 60-year-old man has head and neck cancer with extensive involvement of facial nerves. His pain medications include transdermal fentanyl 100 mcg/hour every 72 hours and oral morphine solution 40 mg every 4 hours as needed. He is still having problems with neuropathic pain. Which treatment is best to recommend?
   A. Begin gabapentin and decrease the dosage of fentanyl.
   B. Increase the dosages of fentanyl and morphine.
   C. Begin diazepam and increase the dosage of fentanyl.
   D. Begin gabapentin and continue fentanyl and morphine at the same dosage.

9. A patient is receiving chemotherapy for limited-stage small cell lung carcinoma. After the third cycle of chemotherapy, she is hospitalized with febrile neutropenia. She recovers, and today she is scheduled to receive the fourth cycle of chemotherapy. Which statement is the best treatment course for this patient?
   A. The patient should receive filgrastim 250 mcg/m^2/day subcutaneously for 10 days, given at least 24 hours after chemotherapy.
   B. The patient should receive filgrastim 5 mcg/kg/day subcutaneously, starting today.
   C. The patient should receive pegfilgrastim 1 mg/day subcutaneously for 6 days, given at least 24 hours after chemotherapy.
   D. The patient should receive filgrastim 5 mcg/kg/day subcutaneously for 7 days, given at least 24 hours after chemotherapy.

10. A 60-year-old woman with breast cancer is to begin chemotherapy with AC (doxorubicin and cyclophosphamide). Laboratory values today include sodium 140 mEq/L, potassium 3.8 mEq/L, glucose 100 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 6 IU/L, alanine aminotransferase 35 IU/L, and total bilirubin 2 mg/dL. Which statement is most appropriate?
    A. The dosage of doxorubicin should be decreased.
    B. The dosage of cyclophosphamide should be decreased.
    C. Both chemotherapy drugs should be given at standard dosages.
    D. Both chemotherapy drugs should be given at decreased dosages.

11. Large cell lymphoma is considered intermediate (between indolent and highly aggressive) in tumor growth and biology. Large cell lymphoma is sensitive to chemotherapy and potentially curable. Metastatic colorectal cancer is considered slow growing. Although responses to chemotherapy commonly occur and chemotherapy can prolong survival (by months), metastatic colorectal cancer is not generally considered curable with chemotherapy. Given these differences between large cell lymphoma and metastatic colorectal cancer, which statement is most accurate?
    A. Patients with large cell lymphoma should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
    B. Patients with metastatic colorectal cancer should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
    C. Patients with large cell lymphoma should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.
    D. Patients with metastatic colorectal cancer should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.

Questions 12 and 13 pertain to the following case.

12. Consider the information provided earlier about large cell lymphoma and metastatic colorectal cancer. Patient 1 with large cell lymphoma is receiving R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) chemotherapy. Patient 2 with metastatic colorectal cancer is receiving FOLFIRI (fluorouracil-leucovorin, irinotecan) chemotherapy. On the day cycle 2 is due, both patients have an ANC of 800 cells/mm^3. Which statement is most appropriate, given the ANC values?
    A. Patient 1 should receive chemotherapy to keep him on schedule because he has a curable disease.
    B. Patient 2 should receive chemotherapy to keep him on schedule because he has a curable disease.
    C. The chemotherapy for patient 1 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.
    D. The chemotherapy for patient 2 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.

13. Sometimes, extravasation is not immediately evident when it occurs. Immediately after patient 1 receives R-CHOP, an extravasation is suspected. Which is the best treatment recommendation for the patient's extravasation?
    A. Application of a warm pack for suspected extravasation of doxorubicin.
    B. Application of a cold pack for suspected extravasation of vincristine.
    C. Parenteral dexrazoxane for suspected extravasation of doxorubicin.
    D. Application of sodium thiosulfate for suspected extravasation of vincristine.

14. A 65-year-old man with metastatic melanoma is being treated with nivolumab and ipilimumab. After treatment cycle 3, he presents to the emergency department with concerns of fatigue and uncontrolled diarrhea. He reports 8 loose stools per day for the past 4 days. On examination, the patient appears dehydrated. Which is the best course of management at this time?
    A. Initiate intravenous fluid replacement and intravenous methylprednisolone 2 mg/kg/day. Patient will need inpatient admission and monitoring until improvement.
    B. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient on loperamide 4 mg by mouth once, followed by 2 mg after each loose stool until symptoms improve.
    C. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient and discontinue immunotherapy.
    D. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient with a prescription for a prednisone taper of 20 mg once daily for 3 days, followed by 15 mg once daily for 3 days, then 10 mg once daily for 3 days, then 5 mg once daily for 3 days, then 2.5 mg for 3 days; then discontinue.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.2 – 1.1.4, 1.1.8 – 1.1.15
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.1 – 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1 – 1.3.5

2. Healthcare Systems and Population Health
    a. 3.1. Implement safe and effective medication use systems to improve healthcare system and population-based outcomes. Sub-task(s): 3.1.1 – 3.1.3
    b. 3.4. Support implementation of pharmacotherapy-related quality improvement projects to foster the safe, effective, and economical use of medications. Sub-task(s): 3.4.1 – 3.4.3

Systems and Patient-Care Problems:

i. Antiemetics
ii. Pain Management
iii. Treatment of Febrile Neutropenia
iv. Use of CSFs in Neutropenia and Febrile Neutropenia
v. Thrombocytopenia
vi. Anemia/Fatigue
vii. Chemoprotectants
viii. Oncology Emergencies

I. ANTIEMETICS

A. Important Definitions Pertaining to Chemotherapy-Induced Nausea and Vomiting (CINV)
   1. Nausea is described as an awareness of discomfort that may or may not precede vomiting; nausea is accompanied by decreased gastric tone and decreased peristalsis.
   2. Retching is the labored movement of abdominal and thoracic muscles associated with vomiting without the expulsion of vomitus (also called dry heaves).
   3. Vomiting (emesis) is the ejection or expulsion of gastric contents through the mouth.
      a. Acute onset: Occurs 0–24 hours after chemotherapy administration and commonly resolves within 24 hours (intensity peaks after 5–6 hours)
      b. Delayed onset: Occurs more than 24 hours after chemotherapy administration
         i. Delayed symptoms are best described with cisplatin, although they are commonly reported in association with other agents (carboplatin or doxorubicin).
         ii. The distinction between acute and delayed symptoms with respect to time of onset is somewhat arbitrary, and it becomes blurred when chemotherapy is administered for several consecutive days.
         iii. The importance of the distinction between acute and delayed (and anticipatory) symptoms is that they likely have different mechanisms and therefore different management strategies.
   4. Anticipatory vomiting (or nausea) is triggered by sights, smells, or sounds and is a conditioned response; it is more likely to occur in patients whose previous post-chemotherapy nausea and vomiting was not well controlled.
   5. Breakthrough emesis occurs despite prophylactic treatment or necessitates additional rescue medications.
   6. Refractory emesis is emesis that occurs during treatment cycles when antiemetic prophylaxis or rescue therapy has failed in previous cycles.

B. Risk Factors for CINV
   1. Patient-related risk factors
      a. Younger age (younger than 50)
      b. Female sex
      c. History of motion sickness
      d. History of nausea or vomiting during pregnancy
      e. Previous history of drug treatment for CINV
      f. Little or no previous alcohol use
      g. Anxiety/high pretreatment expectation of nausea
   2. Emetogenicity of chemotherapy agents: Several schemes for assessing emetogenicity have been proposed.
      a. Originally, emetogenic risk was classified as "none," "mild," "moderate," or "severe."
      b. The Hesketh model, proposed in 1997, classified emetogenic risk as levels ranging from level 1 (less than 10% frequency of emesis) to 5 (more than 90% frequency of emesis).
      c. Current model includes four levels for parenteral chemotherapy and two levels for oral chemotherapy.
      d. Levels for parenteral chemotherapy (e.g., minimal, low, moderate, high emetogenic risk) are defined by the percentage of patients expected to experience emesis when not receiving antiemetic prophylaxis. (See Table 1)
      e. Levels for oral chemotherapy (e.g., prophylaxis recommended or as needed)

3. Radiation therapy can also cause nausea and vomiting. The incidence and severity of radiation-induced nausea and vomiting vary by site of radiation and size of radiation field.
    a. Mildly emetogenic: Radiation to the head and neck or to the extremities
    b. Moderately emetogenic: Radiation to the upper abdomen or pelvis or craniospinal radiation
    c. Highly emetogenic: Total body irradiation, total nodal irradiation, and upper-half-body irradiation

C. General Principles for Managing CINV and Radiation-Induced Nausea and Vomiting
    1. Prevention is the key. Prophylactic antiemetics should be administered before moderately or highly emetogenic agents and before moderately and highly emetogenic radiation.
    2. Antiemetics should be scheduled for delayed nausea and vomiting for select chemotherapy regimens (e.g., cisplatin, doxorubicin/cyclophosphamide (AC)), and rescue antiemetics should be available if prolonged acute symptoms or ineffective antiemetic prophylaxis occurs.
    3. Patients need to be protected throughout the full period of risk for nausea/vomiting:
        a. 3 days for highly emetogenic regimens
        b. 2 days for moderately emetogenic regimens
    4. Begin with an appropriate antiemetic regimen based on the emetogenicity of the chemotherapy drugs.
        a. For multidrug regimens, select antiemetic therapy according to the drug with the highest emetic risk.
        b. The most common antiemetic regimen for highly emetogenic chemotherapy and radiation is the combination of a neurokinin 1 (NK1) receptor antagonist, a serotonin receptor antagonist, and dexamethasone. Adding a corticosteroid to a serotonin receptor antagonist for highly (or moderately) emetogenic anticancer therapy increases efficacy by 10%–20%. Based on randomized clinical trial data, the AC regimen (see Table 1) should always include a three-drug regimen with an NK1 receptor antagonist, a serotonin receptor antagonist, and dexamethasone.
        c. Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines now recommend a four drug regimen for highly emetogenic chemotherapy to include a neurokinin 1 receptor antagonist, a serotonin receptor antagonist, dexamethasone, and olanzapine as the preferred prophylactic regimen. The standard three-drug regimen is still recommended as an option for highly emetogenic chemotherapy.
        d. For moderately emetogenic chemotherapy, the most common antiemetic regimen now includes a serotonin receptor antagonist and dexamethasone. Addition of an NK1 receptor antagonist may be considered after risk stratification.
        e. Single-agent phenothiazine, butyrophenone, or steroids are used for mildly emetogenic regimens and are given on either a scheduled or an as-needed basis for prolonged symptoms (i.e., breakthrough symptoms). Olanzapine is now a preferred option for breakthrough treatment.
        f. Consider using a histamine-2 blocker or proton pump inhibitor for dyspepsia (which can mimic nausea).
        g. Cannabinoids are generally used after other regimens have failed.
        h. Potential drug interactions between antineoplastic agents or antiemetics and other drugs should always be considered. However, no clinically significant drug-drug interactions have emerged to date in randomized clinical trials of anticancer agents with antiemetics. This is likely because of the short duration of antiemetic use in this population.
        i. Follow-up is essential. The response to the emetogenic regimen should always guide the choice of antiemetic regimen for subsequent therapy courses.

D. Emetogenic Potential of Parenteral Chemotherapy Agents

Table 1. Emetogenic Potential of Parenteral Chemotherapy Agents (per NCCN guidelines)

High Emetic Risk (> 90% frequency of emesis)	
AC (combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide)	Doxorubicin ≥ 60 mg/m^2
Carboplatin AUC ≥ 4	Epirubicin > 90 mg/m^2
Carmustine > 250 mg/m^2	Ifosfamide ≥ 2 g/m^2/dose
Cisplatin	Mechlorethamine
Cyclophosphamide > 1500 mg/m^2	Melphalan > 140 mg/m^2
Dacarbazine	Sacituzumab govitecan-hziy
	Streptozocin
Moderate Emetic Risk (30%–90% frequency of emesis)	
Aldesleukin > 12–15 million IU/m^2	Doxorubicin < 60 mg/m^2
Amifostine > 300 mg/m^2	Epirubicin ≤ 90 mg/m^2
Amivantamab-vmjw	Fam-trastuzumab deruxtecan-nxki
Azacitidine	Idarubicin
Bendamustine	Ifosfamide < 2 g/m^2/dose
Busulfan	Irinotecan
Carboplatin AUC < 4	Irinotecan (liposomal)
Carmustine ≤ 250 mg/m^2	Lurbinectedin
Clofarabine	Melphalan < 140 mg/m^2
Cyclophosphamide ≤ 1500 mg/m^2	Methotrexate ≥ 250 mg/m^2
Cytarabine > 200 mg/m^2	Naxitamab-gqgk
Dactinomycin	Oxaliplatin
Daunorubicin	Romidepsin
Dual-drug liposomal encapsulation of cytarabine and daunorubicin	Temozolomide
Dinutuximab	Trabectedin
Low Emetic Risk (10%–30% frequency of emesis)	
Ado-trastuzumab emtansine	Ixabepilone
Aldesleukin ≤ 12 million IU/m^2	Lisocabtagene maraleucel
Amifostine ≤ 300 mg/m^2	Loncastuximab tesirine-lpyl
Arsenic trioxide	Methotrexate > 50 mg/m^2 to < 250 mg/m^2
Axicabtagene ciloleucel	Mitomycin and mitomycin pyelocalyceal solution
Belinostat	Mitoxantrone
Brexucabtagene autoleucel	Mogamulizumab-kpkc
Brentuximab vedotin	Moxetumomab pasudotox-tdfk
Cabazitaxel	Necitumumab
Carfilzomib	Omacetaxine
Copanlisib	Paclitaxel
Cytarabine (low dose) 100–200 mg/m^2	Paclitaxel/albumin
Docetaxel	Pemetrexed
Doxorubicin (liposomal)	Pentostatin
Enfortumab vedotin-ejfv	Polatuzumab vedotin-piiq
Eribulin	Pralatrexate
Etoposide	Tafasitamab-cxix
Floxuridine	Tagraxofusp-erzs
Fluorouracil (5-FU)	Talimogene laherparepvec
Floxuridine	Thiotepa
Gemcitabine	Tisagenlecleucel
Gemtuzumab ozogamicin	Tisotumab vedotin-tftv
Idecabtagene vicleucel	Topotecan
Inotuzumab ozogamicin	Ziv-aflibercept
Isatuximab-irfc	

Table 1. Emetogenic Potential of Parenteral Chemotherapy Agents (per NCCN guidelines) *(Cont'd)*

Minimal Emetic Risk (< 10% frequency of emesis)	
Alemtuzumab	Luspatercept-aamt
Asparaginase	Margetuximab-cmkb
Atezolizumab	Methotrexate ≤ 50 mg/m^2
Avelumab	Nelarabine
Belantamab mafodotin-blmf	Nivolumab
Bevacizumab	Obinutuzumab
Bleomycin	Ofatumumab
Blinatumomab	Panitumumab
Bortezomib	Pembrolizumab
Cemiplimab-rwlc	Pertuzumab
Cetuximab	Pertuzumab/trastuzumab and hyaluronidase-zzxf
Cladribine	Ramucirumab
Cytarabine < 100 mg/m^2	Rituximab
Daratumumab	Rituximab and hyaluronidase
Daratumumab and hyaluronidase-fihj	Siltuximab
Decitabine	Temsirolimus
Denileukin diftitox	Trastuzumab
Dexrazoxane	Trastuzumab and hyaluronidase-oysk
Dostarlimab-gxly	Valrubicin
Durvalumab	Vinblastine
Elotuzumab	Vincristine
Fludarabine	Vincristine (liposomal)
Ipilimumab	Vinorelbine

E. Emetogenic Potential of Oral Chemotherapy Agents (Table 2)

Table 2. Emetogenic Potential of Oral Chemotherapy Agents (per NCCN guidelines)

Moderate to High Emetic Risk (≥ 30% frequency of emesis); Prophylaxis Recommended	
Altretamine	Etoposide
Avapritinib	Fedratinib
Azacytidine	Imatinib > 400 mg/day
Binimetinib	Lenvatinib > 12 mg/day
Bosutinib > 400 mg/day	Lomustine (single day)
Busulfan ≥ 4 mg/day	Midostaurin
Cabozantinib	Mitotane
Ceritinib	Mobocertinib
Crizotinib	Niraparib
Cyclophosphamide ≥ 100 mg/m^2/day	Olaparib
Dabrafenib	Procarbazine
Enasidenib	Rucaparib
Encorafenib	Selinexor
Estramustine	Temozolomide > 75 mg/m^2/day

Table 2. Emetogenic Potential of Oral Chemotherapy Agents (per NCCN guidelines) *(Cont'd)*

Minimal to Low Emetic Risk (< 30% frequency of emesis); As Needed	
Abemaciclib	Melphalan
Acalabrutinib	Mercaptopurine
Afatinib	Methotrexate
Alectinib	Neratinib
Alpelisib	Nilotinib
Asciminib	Osimertinib
Axitinib	Palbociclib
Belzutifan	Pazopanib
Bexarotene	Pemigatinib
Bosutinib ≤ 400 mg/day	Pexidartinib
Brigatinib	Pomalidomide
Busulfan < 4 mg/day	Ponatinib
Capecitabine	Pralsetinib
Capmatinib	Regorafenib
Chlorambucil	Ribociclib
Cobimetinib	Ripretinib
Cyclophosphamide < 100 mg/m^2/day	Ruxolitinib
Dacomitinib	Selpercatinib
Dasatinib	Sonidegib
Decitabine and cedazuridine	Sorafenib
Duvelisib	Sotorasib
Entrectinib	Sunitinib
Erdafitinib	Talazoparib tosylate
Erlotinib	Tazemetostat
Everolimus	Temozolomide ≤ 75 mg/m^2/day
Fludarabine	Tepotinib
Gefitinib	Thalidomide
Gilteritinib	Thioguanine
Glasdegib	Tivozanib
Hydroxyurea	Topotecan
Ibrutinib	Trametinib
Idelalisib	Tretinoin
Infigratinib	Trifluridine/tipiracil
Imatinib ≤ 400 mg/day	Tucatinib
Ivosidenib	Umbralisib
Ixazomib	Vandetanib
Lapatinib	Vemurafenib
Larotrectinib	Venetoclax
Lenalidomide	Vismodegib
Lenvatinib ≤ 12 mg/day	Vorinostat
Lorlatinib	Zanubrutinib

F. Antiemetics
   1. Serotonin-3 receptor antagonists (dolasetron, granisetron, ondansetron, and palonosetron)
      a. Mechanism of action (MOA): Block serotonin receptors peripherally in the gastrointestinal tract and centrally in the medulla
      b. Adverse events: Headache and constipation, occurring in 10%–15% of patients. May increase liver function tests and cause QT prolongation (especially with high dosages or intravenous push administration).

c. Dolasetron, granisetron, ondansetron, and palonosetron are considered equally efficacious at equivalent dosages. Therefore, the antiemetic drug of choice is often based on cost and organizational contract.
d. Dosage forms: Granisetron and ondansetron are available in oral and parenteral forms (including an orally disintegrating tablet for ondansetron). Dolasetron is now indicated only in CINV in its oral form. Granisetron is also available in a transdermal patch (34.3 mg applied about 24–48 hours before the first dose of chemotherapy; maximal duration of patch is 7 days) as well as an extended-release subcutaneous formulation (10 mg at least 30 minutes before first dose of chemotherapy; not to be administered more often than every 7 days).
e. Palonosetron is indicated to prevent acute CINV for highly emetogenic chemotherapy and acute and delayed CINV for moderately emetogenic chemotherapy.
    i. Half-life: About 40 hours (longer compared with other serotonin antagonists)
    ii. Dosage: 0.25 mg intravenous push 30 minutes before chemotherapy administration
    iii. An oral capsule form is available but only as a combination product with an NK1 antagonist (netupitant/palonosetron).
    iv. One dose may be used before the start of a 3-day chemotherapy regimen instead of several daily doses of oral or parenteral serotonin-3 receptor antagonists.
    v. Adverse events: Headache and constipation (same as other serotonin antagonists)

2. Corticosteroids (dexamethasone, methylprednisolone)
    a. MOA: Unknown; thought to act by inhibiting prostaglandin synthesis in the cortex
    b. Adverse effects associated with single doses and short courses of steroids are infrequent; they may include euphoria, anxiety, insomnia, increased appetite, and mild fluid retention; rapid parenteral administration may be associated with transient and intense perineal, vaginal, or anal burning.
    c. Dexamethasone has been studied more often in clinical trials than methylprednisolone.
    d. Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy.
    e. Corticosteroid antiemetic premedication should be avoided for 3–5 days before and 90 days after CAR (chimeric antigen receptor) T-cell therapies. Antiemetic regimens used during lymphodepleting chemotherapy regimens should also use a corticosteroid-sparing approach to antiemetic prophylaxis.
3. NK1 receptor antagonists (aprepitant, aprepitant injectable emulsion, fosaprepitant, rolapitant)
    a. All NK1 receptor antagonists must be used in combination with a serotonin receptor antagonist and dexamethasone and are approved for preventing acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy known to cause these problems, including highly emetogenic chemotherapy.
    b. MOA: Aprepitant is a selective high-affinity antagonist of human substance P/NK1.
    c. Aprepitant improved the overall complete response (defined as no emetic episodes and no use of rescue therapy) by about 20% when added to a serotonin receptor antagonist and dexamethasone.
    d. Aprepitant oral dosage: 125 mg on day 1, then 80 mg on day 2 and 80 mg on day 3. Intravenous aprepitant dosing is 130 mg on day 1 only for highly emetogenic chemotherapy and 100 mg on day 1 only for moderately emetogenic chemotherapy.
    e. Fosaprepitant dosage (prodrug): 150 mg intravenously on day 1 only (parenteral formulation)
    f. Metabolized primarily by cytochrome P450 (CYP) 3A4 (all NK1 agents), with aprepitant and fosaprepitant having minor metabolism by CYP1A2 and CYP2C19
        i. Dexamethasone: Fosaprepitant and aprepitant may increase area under the curve of dexamethasone. Decrease dosage by about 40% on day 2 or 3 if dexamethasone given orally (not necessary if given intravenously because of first-pass metabolism). Rolapitant does not inhibit dexamethasone metabolism.

ii. Oral contraceptives: May reduce the effectiveness of oral contraceptives. Would recommend another form of birth control for women of childbearing age when taking with aprepitant/fosaprepitant
iii. Warfarin: May decrease international normalized ratio (clinically significant). After receiving fosaprepitant or aprepitant, patients should have their international normalized ratios checked within 7–10 days.
iv. Caution NK1 use in patients with lymphoma: Studies suggest neuropathy is more common in patients on R-CHOP receiving aprepitant, because of aprepitant's CYP3A4 inhibition. Other NK1 agents have CYP3A4 inhibition, and caution should be used with these as well.

g. Adverse events: Asthenia, dizziness, and hiccups
h. MOA: Rolapitant substance P/NK1 receptor antagonist indicated in combination with dexamethasone and serotonin antagonist in adults with cancer for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy.
i. Rolapitant dosage: 180 mg orally on day 1 only
j. Adverse events: Loss of appetite, neutropenia, and hiccups

4. NK1 receptor antagonist/serotonin-3 combination (netupitant/palonosetron and fosnetupitant/palonosetron)
   a. MOA: Fixed combination of netupitant/fosnetupitant, a substance P/NK1 receptor antagonist, and palonosetron, a serotonin-3 receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase, and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phases after cancer chemotherapy.
   b. Netupitant/palonosetron dosage: 1 capsule once on day 1 (capsule contains 300 mg of netupitant/palonosetron 0.5 mg)
   c. Fosnetupitant/palonosetron dosage: Intravenously once daily on day 1 (contains 235 mg of fosnetupitant/palonosetron 0.25 mg)
   d. Adverse effects: Headache, asthenia, dyspepsia, fatigue, constipation, and erythema
   e. Caution in patients with hepatic dysfunction, severe renal impairment, or end-stage renal disease
5. Benzamide analogs (metoclopramide)
   a. MOA: Blockade of dopamine receptors in the chemoreceptor trigger zone; stimulation of cholinergic activity in the gut, increasing (forward) gut motility; and antagonism of peripheral serotonin receptors in the intestines. These effects are dose related.
   b. Adverse events: Mild sedation and diarrhea, as well as extrapyramidal reactions (e.g., dystonia, akathisia), which may be mitigated by diphenhydramine or benztropine.
   c. Historically, higher dosages of metoclopramide were used for desired results (1–2 mg/kg intravenously). Guidelines now recommend 10–20 mg every 6 hours, if needed.
6. Phenothiazines (prochlorperazine, chlorpromazine, promethazine)
   a. MOA: Block dopamine receptors in the chemoreceptor trigger zone
   b. Adverse events: Drowsiness, hypotension, akathisia, and dystonia
7. Butyrophenones (haloperidol, droperidol)
   a. MOA: Similar to phenothiazines
   b. They are at least as effective as the phenothiazines, and some studies indicate they are superior; they offer a different chemical structure that may bind differently to the dopamine receptor and offer an initial alternative when a phenothiazine fails.
   c. Adverse events: Sedation; hypotension is less common than with phenothiazines; extrapyramidal symptoms are also seen.
   d. The use of droperidol as an antiemetic has fallen out of favor because of the risk of QT prolongation or torsades de pointes.

8. Benzodiazepines (lorazepam)
    a. Lorazepam as a single agent has minimal antiemetic activity. However, several properties make lorazepam useful in combination with or as an adjunct to other antiemetics.
        i. Anterograde amnesia helps prevent anticipatory nausea and vomiting.
        ii. Relief of anxiety
        iii. Management of akathisia caused by phenothiazines, butyrophenones, or metoclopramide
        iv. Adverse events: Amnesia, sedation, hypotension, perceptual disturbances, and urinary incontinence. Note that amnesia and sedation may, in fact, be desirable.
9. Atypical antipsychotic (olanzapine)
    a. Approved by the U.S. Food and Drug Administration (FDA) to treat schizophrenia and bipolar disorder, this thienobenzodiazepine is used off label as an alternative agent for preventing nausea and vomiting in highly emetogenic regimens and may be used as an option for breakthrough nausea and vomiting.
    b. MOA: Blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine
    c. Adverse effects: Sedation, dry mouth, increased appetite, weight gain, postural hypotension, QTc prolongation, and dizziness
    d. Olanzapine has been associated with an elevated risk of hyperlipidemia, hyperglycemia, and new-onset diabetes. Use with caution in older adults because olanzapine use in this patient population has been associated with an elevated risk of death and an elevated incidence of cerebrovascular adverse events in patients with dementia-related psychosis (black box warning)
    e. A phase III study compared olanzapine with aprepitant in highly emetogenic chemotherapy regimens. Overall response rates were similar in both groups for acute and delayed nausea and vomiting. The proportion of patients without nausea was similar between the two groups in the acute period but was higher in the olanzapine arm in the delay period, resulting in a higher rate of nausea control. As an alternative to, or in combination with, aprepitant, an olanzapine-based regimen is an option in highly or moderately emetogenic regimens according to the most recent National Comprehensive Cancer Network (NCCN) guidelines.
10. Cannabinoids (dronabinol, nabilone)
    a. MOA: Cannabinoid receptors may mediate at least some of the antiemetic activity of this class of agents. Additional antiemetic mechanisms that have been proposed include inhibition of prostaglandins and blockade of adrenergic activity.
    b. Adverse events: Drowsiness, dizziness, euphoria, dysphoria, orthostatic hypotension, ataxia, hallucinations, and time disorientation

G. Emesis Prevention Algorithms (Tables 3 and 4)

Table 3. Emesis Prevention Algorithm for Parenteral Chemotherapy (per NCCN Guidelines)[a]

Level of Emetogenicity	Emesis Treatment Day 1	Emesis Treatment Days 2, 3, and 4
High	NK1 antagonist - Aprepitant 125 mg PO once - Aprepitant injectable emulsion 130 mg IV once - Fosaprepitant 150 mg IV once - Netupitant 300 mg/palonosetron 0.5 mg combination PO once - Fosnetupitant 235 mg/palonosetron 0.25 mg combination IV once - Rolapitant 180 mg PO once AND Serotonin-3 antagonist AND Dexamethasone 12 mg PO/IV once ± Olanzapine 5–10 mg PO once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor OR Olanzapine-containing regimen: 1. Olanzapine 5–10 mg PO once 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg PO/IV once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	- Aprepitant 80 mg PO daily on days 2 and 3 (only if aprepitant PO used on day 1) - Dexamethasone 8 mg PO/IV daily on days 2, 3, 4 - Olanzapine 5–10 mg PO daily on days 2, 3, 4 (if olanzapine PO used on day 1) OR Olanzapine 5–10 mg PO days 2–4
Moderate	Serotonin-3 antagonist AND Dexamethasone 12 mg PO/IV once WITH/WITHOUT NK1 antagonist PO/IV (may consider adding NK1 for patients with additional risk factors or previous treatment failure with serotonin-3 antagonist and dexamethasone) ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor OR Olanzapine-containing regimen: 1. Olanzapine 5–10 mg PO once 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg IV once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	Serotonin-3 antagonist OR Steroid monotherapy Dexamethasone 8 mg PO/IV daily on days 2, 3 OR - If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV days 2, 3 - If fosaprepitant or rolapitant given day 1, no further NK1 antagonists needed on days 2 and 3 ± dexamethasone days 2, 3 OR Olanzapine-containing regimen: Olanzapine 5–10 mg PO days 2, 3

Table 3. Emesis Prevention Algorithm for Parenteral Chemotherapy (per NCCN Guidelines) *(Cont'd)*

Level of Emetogenicity	Emesis Treatment Day 1	Emesis Treatment Days 2 and 3
Low	Dexamethasone 8-12 mg PO/IV once OR Metoclopramide 10-20 mg PO/IV once OR Prochlorperazine 10 mg PO/IV once OR Serotonin-3 antagonists (oral therapy) ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	Repeat day 1 selection daily for multi-day doses of chemotherapy only
Minimal	No routine prophylaxis	No routine prophylaxis

[a]A four-drug regimen containing an NK1 antagonist, a serotonin antagonist, dexamethasone, and olanzapine is now the preferred first-line prophylactic option for highly emetogenic regimens according to the most recent NCCN and ASCO antiemetic guidelines.

IV = intravenous(ly); NK1 = neurokinin 1; PO = orally.

Table 4. Emesis Prevention Algorithm for Oral Chemotherapy per NCCN Guidelines

Level of Emetogenicity	Emesis Treatment (start before chemotherapy and continue daily)
Moderate to high emetic risk	Serotonin-3 antagonist (choose one): Dolasetron 100 mg daily Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-hr transdermal patch every 7 days Ondansetron 8-16 mg PO daily ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor
Minimal to low emetic risk	Metoclopramide 10–20 mg PO and then q6hr PRN OR Prochlorperazine 10 mg PO and then q6hr PRN (maximum 40 mg/day) OR Serotonin-3 antagonist (choose one): Dolasetron 100 mg PO daily PRN Granisetron 1-2 mg (total dose) PO daily PRN Ondansetron 8–16 mg PO daily PRN ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor

BID = twice daily; PRN = as needed; q = every.

Patient Case

Questions 1 and 2 pertain to the following case.

A 60-year-old woman was recently given a diagnosis of advanced non–small cell lung cancer. She will begin treatment with cisplatin 100 mg/m^2 plus vinorelbine 30 mg/m^2.

1. Which is the most appropriate antiemetic regimen for preventing acute emesis?
   A. Aprepitant plus palonosetron plus dexamethasone.
   B. Aprepitant plus prochlorperazine plus dexamethasone.
   C. Aprepitant plus granisetron plus ondansetron.
   D. Lorazepam plus ondansetron plus metoclopramide.

2. If the patient has anticipatory nausea and vomiting with her next cycle, which regimen would be most appropriate?
   A. Aprepitant plus palonosetron plus dexamethasone.
   B. Aprepitant plus prochlorperazine plus dexamethasone.
   C. Aprepitant plus granisetron plus metoclopramide.
   D. Aprepitant plus ondansetron plus dexamethasone plus lorazepam.

II. PAIN MANAGEMENT

A. Principles of Cancer Pain Management
   1. The most important step in treating pain is the assessment.
   2. The oral route is preferred, when available. Although the ratio of oral to parenteral potency of morphine is commonly 6:1, clinical observation of chronic morphine use indicates that this ratio is closer to 3:1.
   3. Choose the analgesic drug and dosage to match the patient's degree of pain.
   4. For persistent severe pain, use a product with a long duration of action. Pain medications should always be administered on a scheduled basis or around the clock, not as needed.
      a. It is always easier to prevent pain from recurring than to treat it once it has recurred.
      b. As-needed dosing should be used for breakthrough pain, which is pain that "breaks through" the regularly scheduled opioid; an immediate-release, short-acting opioid should always accompany a long-acting opioid.
   5. Reevaluate pain and pain relief often, especially when initiating pain therapy; if more than two as-needed doses are necessary for breakthrough pain in a 24-hour period, consider modifying the regimen. Before adding or changing to another drug, maximize the dosage and schedule of the current analgesic drug.
   6. Provide medications to prevent other potential side effects from opioid therapy (e.g., constipation).
   7. Use appropriate adjuvant analgesics and nondrug measures to maximize pain control.
   8. Goals of pain management (The "5 A's")
      a. Optimize analgesia.
      b. Optimize activities of daily living.
      c. Minimize adverse effects.
      d. Avoid aberrant drug taking.
      e. Relationship between pain and mood (affect)
   9. Survival is linked to symptom control and pain management, which contribute to broad quality-of-life improvement.

10. For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission.
11. Optimal use of disease-specific therapies is essential to managing tumor-related pain.

B. Diagnosis and Assessment of Pain
   1. Best addressed by proper pain assessment including comprehensive history and physical examination
   2. Evaluation of pain management: Pain intensity, pain relief, and medication adverse effects or allergies must be assessed and reassessed.
   3. Objective observations such as grimacing, limping, or tachycardia may be helpful in assessment.
   4. Clinicians must accept the patient's report of pain.

C. Pain Rating Scales
   1. Use pain assessment tools to evaluate pain intensity at baseline and to assess how well a pain medication regimen is working.
      a. Numeric rating scale of 0–10, with 0 = no pain and 10 = worst pain imaginable
      b. Pediatric patients: Faces-of-Pain Scale, poker chip method
   2. Because pain is subjective, it is best evaluated by the patient (i.e., not a caregiver and not the health professional).

D. Treatment of Pain: The Analgesic Ladder
   1. For mild pain (pain rating of 1–3 on a 10-point scale), the first step is a nonopioid analgesic drug: Nonsteroidal anti-inflammatory drug (NSAID), aspirin, or acetaminophen, or consider slow titration of short-acting opioids either as needed or as scheduled.
   2. For persistent or moderate pain (pain rating of 4–7 on a 10-point scale), add a weak opioid: Codeine or hydrocodone, available in combination with nonopioid analgesic drugs. Slow titration of a short-acting opioid may also be considered and should be administered every 3–4 hours as needed. If four or more doses of a short-acting opioid are consistently needed per day, consider adding or increasing the dose of a long-acting opioid on the basis of the total daily dose.
   3. For persistent or for severe pain (pain rating of 8 or greater on a 10-point scale), replace the weak opioid with a strong opioid: Morphine, oxycodone, or similar drug. In opioid-naive patients experiencing severe pain, short-acting opioids should be rapidly titrated. Once a patient with persistent pain is taking stable dosages of short-acting opioids, the drug should be changed to an extended-release or long-acting formulation with breakthrough short-acting opioids. When converting to long-acting opioids, the initial range will be around 50%–100% of the usual daily requirement (depending on expected pain natural history).
   4. For acute, severe pain crisis, consider hospital or inpatient hospice admission to achieve patient-specific goals for comfort and function.

E. Nonopioid Analgesics: NSAIDs
   1. MOA: Act peripherally to inhibit the activity of prostaglandins in the pain pathway
   2. There is a ceiling effect to the analgesia provided by NSAIDs.
   3. Adverse events: Consider inhibition of platelet aggregation and the effects of inhibition of renal prostaglandins. NSAIDs in patients with hematologic disorders are generally not recommended because of platelet inhibition. In addition, there are concerns about the possibility that NSAIDs will mask fever in a patient with neutropenia who is potentially febrile. All NSAIDs with systemic administration have been associated with renal toxicities.
   4. Remember, NSAIDs are generally used in addition to, not instead of, opioids.
   5. NSAIDs are often used for patients with metastatic bone pain.

F. Nonopioid/Opioid Combinations
   1. Aspirin or acetaminophen or ibuprofen plus codeine or hydrocodone or oxycodone is commonly used.
   2. Be aware of the risk of acetaminophen overdose with these products. As with any combination product, dosage escalation of one component necessitates escalation of the others. For patients needing high dosages, pure opioids are preferred.
   3. Oxycodone/acetaminophen is available in several strengths; however, use caution when taking multiple tablets per day because of the acetaminophen daily maximum recommendations.

G. Opioid Analgesics
   1. Mechanism: Opioids act centrally in the brain (periaqueductal gray region) and at the level of the spinal cord (dorsal horn) at specific opioid receptors.
   2. The opioids have no analgesic ceiling.
   3. Morphine
      a. Morphine is the standard with which all other drugs are compared; opioids may differ in duration of action, relative potency, oral effectiveness, and adverse event profiles, but none is clinically superior to morphine.
      b. Flexibility in dosage forms and administration routes: Oral (sustained release, immediate release), sublingual, parenteral, intrathecal/epidural, subcutaneous, and rectal
      c. Long duration of action: Sustained-release products last 8–12 hours or, for some preparations, 24 hours.
      d. Morphine is one of the least expensive opioids, but it should be used with caution in patients with renal dysfunction because of the metabolite.
   4. Oxycodone
      a. Available in oral formulation only
      b. Available as a single drug (i.e., not in combination) in both long- and short-acting formulations
      c. Alternative to morphine in the setting of renal dysfunction
   5. Fentanyl
      a. Fentanyl is available as a parenteral formulation; a sublingual, intranasal, or transdermal preparation; an oral transmucosal preparation; and a buccal tablet. Transmucosal and buccal fentanyl are used for breakthrough pain.
      b. Each transdermal patch provides sustained release of drug and can provide pain relief for 48–72 hours. These should not be used in opioid-naive patients.
      c. Consider the implications for dosing transdermal fentanyl in cachectic patients: Fentanyl initially forms a depot in subcutaneous tissue, and patients with little or no fat may not achieve pain relief or may achieve only inconsistent pain relief.
      d. Slow onset and long elimination after patch application and removal, respectively
      e. Bioavailability is greater with buccal tablets than with the transmucosal preparation; thus, equivalent dosages are higher for transmucosal and lower for buccal tablets.
   6. Hydromorphone
      a. Available in parenteral and oral formulations (short- and long-acting)
      b. Considered a semisynthetic compound
      c. Alternative to morphine with higher potency
      d. Alterative option in patients with renal dysfunction
   7. Oxymorphone
      a. Semisynthetic opioid analgesic
      b. Most commonly seen as immediate- and extended-release tablets
      c. Used for moderate to severe pain
      d. Should not be implemented in patients who are not currently on an opioid regimen
      e. On June 8, 2017, the FDA has requested that the extended-release formulation of oxymorphone be removed from the market because of risks related to abuse.

8. Methadone
    a. Semisynthetic used in maintenance treatment for opioid-dependent patients and as an effective analgesic in patients taking opioids long term for moderate to severe pain
    b. Has activity not only at the opioid receptors but also at the *N*-methyl-D-aspartate receptor, which may confer benefit to patients with neuropathic pain
    c. Complex pharmacokinetics with extended half-life (8–59 hours), which creates difficulties in dosing and transitioning from one opioid to another
    d. Associated with QT prolongation and torsades de pointes
    e. Start low and titrate slowly (only escalating after 3–5 days) because of the changing conversion ratios with increasing morphine equivalents.
    f. If using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain
9. Adverse events
    a. Sedation: Tolerance usually develops within several days; remember that more sedation may be expected in a patient who has been unable to sleep because of uncontrolled pain. For patients who are intolerant of sedation and have good pain control, a dosage reduction may be considered. If dosage reduction compromises pain control, adding a stimulant (e.g., dextroamphetamine, methylphenidate) may be considered. Other central nervous system adverse events include dysphoria and hallucinations.
    b. Constipation is very common, and tolerance does not develop to this effect. Decreased intestinal peristalsis is caused by decreased intestinal tone; delayed gastric emptying may also occur. Regular use of stool softeners in addition to a stimulant laxative is imperative to manage constipation.
    c. Nausea and vomiting are common. As seen with sedation, tolerance develops within about a week. Nausea and vomiting may have a vestibular component, developing as pain relief promotes increased mobility. Agents used in the treatment of vertigo (e.g., meclizine, dimenhydrinate) may be useful in managing the vestibular component, although these agents should be used with caution because combination use with opioids may increase sedation. Nausea and vomiting may also occur because of stimulation of the chemoreceptor trigger zone. Drugs that block dopamine receptors (e.g., phenothiazines) provide relief of this component of nausea and vomiting until tolerance develops.
    d. Urinary retention and bladder spasm are more common in older adults and in patients taking long-acting formulations.

H. Bisphosphonates
1. Bisphosphonates decrease the worsening of pain by preventing disease progression in the bone and the number of skeletal-related events in patients with bone metastases from solid tumors or osteolytic lesions from multiple myeloma when given for 1 year. Skeletal-related events include pathologic fracture, need for radiation therapy to bone, surgery to bone, and spinal cord compression.
2. Most recently updated in October 2017 the American Society of Clinical Oncology published initial guidelines for the use of bisphosphonates in breast cancer.
    a. It is recommended that patients with breast cancer who have evidence of bone metastases on plain radiographs receive either pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks. Dosage adjustments for renal dysfunction are necessary according to package insert recommendations.
    b. Women with abnormal bone scan and abnormal computed tomographic scan or magnetic resonance imaging showing bone destruction but a normal radiograph should also receive the previously recommended bisphosphonates.
    c. Therapy should continue until the patient has evidence of a substantial decline in performance status.
    d. Bisphosphonates may be used in combination with other pain therapies in patients with pain caused by osteolytic disease.

e. A new guideline for adjuvant bisphosphonate use in breast cancer by the American Society of Clinical Oncology published in March 2017 recommends that zoledronic acid 4 mg over 15 minutes every 6 months be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy.

3. Most recently updated in 2018, the American Society of Clinical Oncology published guidelines for the use of bisphosphonates in multiple myeloma.
   a. Patients with lytic bone destruction seen on plain radiographs should receive either pamidronate 90 mg intravenously over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks (dosing once every 3 months may be considered in patients with stable/responsive disease).
   b. Therapy should continue until there is evidence of substantial decline in a patient's performance status.
   c. Patients with osteopenia but no radiologic evidence of bone metastases or compression fracture can receive bisphosphonates.
   d. Bisphosphonates are not recommended for patients with solitary plasmacytoma, smoldering or indolent myeloma, or monoclonal gammopathy of undetermined significance.
   e. Bisphosphonates may be used in patients with pain caused by osteolytic disease.
4. Standard dosing for bisphosphonates in solid tumor metastases is once every 3–4 weeks. However, recent data analyses have supported less-frequent dosing. Dosing once every 12 weeks did not increase the risk of skeletal events within 2 years in patients with at least one site of bone involvement compared with once-every-4-week dosing.
5. Adverse events: Low-grade fevers, nausea, anorexia, vomiting, hypomagnesemia, hypocalcemia, hypokalemia, nephrotoxicity, and atypical femur fractures
   a. Serum creatinine should be monitored before each dose (see package insert for specific recommendations).
   b. Package insert recommends initiating patients on oral calcium 500 mg plus vitamin D 400 international units/day to prevent hypocalcemia.
   c. Several reports of osteonecrosis of the jaw occurring in patients receiving bisphosphonates have appeared in the literature. Osteonecrosis of the jaw usually follows a dental procedure or dental disorder. The long half-life of bisphosphonates in bone makes this adverse event difficult to prevent and manage. Patient education and education of dentists are important. Patients should have a dental examination with preventive dentistry before treatment with bisphosphonates.

I. Receptor Activator of NF-κB Ligand (RANKL) Inhibitor
   1. Denosumab: Fully human monoclonal antibody that targets and inhibits RANKL, a protein that acts as the primary signal to promote bone removal
   2. Indication: Prevention of skeletal-related events in patients with bone metastases from solid tumors and in patients with multiple myeloma.
   3. Dosage: 120 mg subcutaneously every 4 weeks
   4. Adverse events: Urinary and respiratory tract infections, cataracts, constipation, rashes, hypocalcemia (especially in patients with CrCl less than 30 mL/minute), osteonecrosis of the jaw, and joint pain
   5. Contraindications: Hypocalcemia. Patients should be taking calcium and vitamin D.
   6. No adjustment for hepatic or renal dysfunction is needed.

J. Adjuvant analgesics are drugs whose primary indication is other than pain; they are used to manage specific pain syndromes. Most often, adjuvant analgesics are used in addition to, rather than instead of, opioids.
   1. Antidepressants (e.g., amitriptyline, duloxetine) and anticonvulsants (e.g., gabapentin, carbamazepine, pregabalin) are used for neuropathic pain (e.g., phantom limb pain, nerve compression caused by tumor).
   2. Transdermal lidocaine is useful in localized neuropathic pain.
   3. Corticosteroids are useful in pain caused by nerve compression or inflammation, lymphedema, bone pain, or elevated intracranial pressure.

4. Benzodiazepines: Diazepam, lorazepam. Useful for muscle spasms; baclofen is another alternative for intractable muscle spasms
5. Strontium-89: Radionuclide for treatment of bone pain caused by osteoblastic lesions; a single dose may provide relief for several weeks or even months; however, it is myelosuppressive.
6. NSAIDs are recommended for treating pain caused by bone metastases. Prostaglandins sensitize nociceptors (pain receptors) to painful stimuli, thus providing a rationale for using NSAIDs.

K. Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release/Long-Acting Opioid Analgesics
   1. On June 9, 2012, the FDA announced it would require manufacturers of extended-release and long-acting opioid analgesics to provide training for health care professionals who prescribe these agents.
   2. Components of the REMS program
      a. Prescriber education: Information on extended-release or long-acting opioid analgesics; information on assessing patients for treatment with these drugs; initiating therapy, modifying dosing, and discontinuing use of extended-release or long-acting opioid analgesics; managing therapy and monitoring patients; and counseling patients and caregivers about the safe use of these drugs. Prescribers will also learn how to recognize evidence of potential opioid misuse, abuse, and addiction.
      b. Patient counseling: Patient counseling documents for providers will be developed to assist prescribers in counseling patients about their responsibilities for using these medications safely. Patients will receive an updated medication guide, together with their prescription, that contains information on the safe use and disposal of extended-release or long-acting opioid analgesics from their pharmacist. Guide will include instructions for patients to consult their health care professional before changing dosages, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure of family members.
      c. Short-acting opioid products are not included in this program.

Patient Case

Questions 3 and 4 pertain to the following case.

A 75-year-old man has metastatic prostate cancer. The main sites of metastatic disease are regional lymph nodes and bone (several hip lesions). He has aching pain with occasional shooting pains. The latter are thought to be the result of nerve compression by enlarged lymph nodes. He has been taking oxycodone/acetaminophen 5 mg/325 mg 2 tablets every 4 hours and ibuprofen 400 mg every 8 hours. His current pain rating is 8/10, and he states that his pain cannot be controlled.

3. Which is the best recommendation to manage his pain at this time?
   A. Increase oxycodone/acetaminophen to 7.5 mg/325 mg, 2 tablets every 4 hours.
   B. Increase oxycodone/acetaminophen to 10 mg/325 mg, 2 tablets every 4 hours.
   C. Discontinue oxycodone/acetaminophen, discontinue ibuprofen, and add morphine sustained release every 12 hours.
   D. Discontinue oxycodone/acetaminophen and add morphine sustained release every 12 hours.

4. Which is the most appropriate adjunctive medication for this patient's pain?
   A. Naproxen.
   B. Single-agent (single ingredient) acetaminophen.
   C. Gabapentin.
   D. Baclofen.

III. TREATMENT OF FEBRILE NEUTROPENIA

A. Principles of Chemotherapy-Induced Bone Marrow Suppression
   1. Bone marrow suppression is the most common dose-limiting toxicity associated with traditional cytotoxic chemotherapy.
   2. WBC = Usual range of 4.8–10.8 × 100 cells/mm^3 with a circulating life span of 6–12 hours; decreased WBC = leucopenia or granulocytopenia; the risk is life-threatening infections; the risk increases with absolute neutrophil count (ANC) less than 500 cells/mm^3, and the risk is greatest with ANC less than 100 cells/mm^3. Because neutrophils have the fastest turnover, the effects of cytotoxic chemotherapy are greatest on neutrophils (compared with platelets or red blood cells [RBCs]).
      a. The nadir (usually defined by the ANC) is the lowest value to which the blood count falls after cytotoxic chemotherapy. Usually occurs 10–14 days after chemotherapy administration, with counts usually recovering by 3–4 weeks after chemotherapy; exceptions include mitomycin, decitabine, azacitidine, bleomycin, vincristine, and nitrosoureas (carmustine and lomustine), which have nadirs of 28–42 days after chemotherapy and recovery of neutrophils 6–8 weeks after treatment
      b. General rule for calculating ANC: ANC = WBC × percentage granulocytes or neutrophils (segmented neutrophils plus band neutrophils). Example: A patient's WBC = 4500 cells/mm^3 with 10% segmented neutrophils and 5% band neutrophils. What is the ANC? 4500 × (0.1 + 0.05) = 675 cells/m^3.
      c. To receive chemotherapy, in general, a patient should have a WBC greater than 3000 cells/mm^3 or an ANC greater than 1000 cells/mm^3 and a platelet count of 100,000 cells/mm^3 or more. In some protocols, consideration of the patient's clinical status and FDA labels or package inserts specify different (lower) thresholds for administering chemotherapy; if cytopenia is attributable to disease in the bone marrow, chemotherapy (full dose) may in fact be indicated and will normalize cytopenia when disease improves with treatment; some drugs are nonmyelosuppressive (e.g., vincristine, bleomycin, monoclonal antibodies).
      d. The potential curability of the disease influences what action will be taken during the next cycle of chemotherapy, either dosage reduction of myelosuppressive chemotherapy (palliative intent) or support with a CSF (curative intent). Exceptions to the use of CSFs in the curative setting exist because of potential toxicities with various regimens. Use of CSFs is usually avoided in Hodgkin lymphoma with the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen because various retrospective studies have found that patients receiving ABVD who develop neutropenia rarely develop infection complications and appear to have the potential for increased pulmonary toxicities with bleomycin if CSFs are used.
   3. Other factors affecting myelosuppression include previous chemotherapy, previous radiation therapy, and direct bone marrow involvement by tumor. The development of rare blood disorders (e.g., thrombotic microangiopathy or disseminated intravascular coagulation) must be ruled out in patients with malignancies who received myelosuppressive chemotherapy but experienced an unexplained delay in recovery of platelets and hemoglobin.

B. Neutropenia and Febrile Neutropenia
   1. Infectious Diseases Society of America guidelines for antibiotic use were updated in 2010.
   2. Neutropenia is defined as an ANC of 500 cells/mm^3 or less or a count of less than 1000 cells/mm^3, with a predicted decrease to less than 500 cells/mm^3 during the next 48 hours.
   3. Febrile neutropenia is defined as neutropenia and a single oral temperature of 101°F or more or a temperature of 100.4°F or more for at least 1 hour.
   4. Neutropenic patients are at an elevated risk of developing serious and life-threatening infections.
   5. The usual signs and symptoms of infection (e.g., abscess, pus, infiltrates on chest radiograph) are absent, with fever often being the only indicator. In addition, cultures are typically negative. Therefore, febrile neutropenia necessitates prompt investigation and treatment.

6. Treatment of patients with febrile neutropenia includes a risk assessment for complications and severe infection.
    a. Characteristics of low-risk neutropenia include the following: ANC of 100 cells/mm^3 or more and absolute monocyte count of 100 cells/mm^3 or more, normal chest radiograph, almost normal renal and hepatic function, severe neutropenia (100 cells/mm^3 or less) for less than 7 days and resolution expected in less than 10 days, no parenteral access site or catheter site infection, early evidence of bone marrow recovery, malignancy in remission, peak oral temperature of less than 102°F, no neurologic or mental status changes, no appearance of illness, absence of abdominal pain, and no comorbid complications (e.g., shock, hypoxia, pneumonia, other deep organ infection, vomiting, diarrhea).
    b. The Multinational Association for Supportive Care in Cancer has developed a scoring index to help identify patients with low-risk febrile neutropenia. Scores are assessed on the basis of factors such as those listed previously. A MASCC risk index score of less than 21 indicates high-risk febrile neutropenia, whereas a score of 21 or greater indicates low-risk febrile neutropenia.
    c. The Clinical Index of Stable Febrile Neutropenia (CISNE) provides another risk categorization for risk of serious complications, including mortality in patients with neutropenic fever. Risk stratification is validated in adults. A CISNE score of 3 or greater indicates high-risk febrile neutropenia, and a score of less than 3 indicates low-risk febrile neutropenia.
    d. Febrile neutropenia that is considered to carry a low risk of complications may be treated with either oral or parenteral antibiotics in an outpatient or inpatient setting.
    e. Patients with high-risk febrile neutropenia (i.e., patients who do not have low-risk characteristics, as noted earlier) should receive parenteral antibiotics in the hospital.
7. Considerations in the initial selection of an antibiotic include the potential infecting organism, potential sites and source of infection, local antimicrobial susceptibilities, and organ dysfunction potentially affecting antibiotic clearance or toxicity, and drug allergy. The most common source of infection is endogenous flora, which could be gram-negative or gram-positive bacteria; the more prolonged the neutropenia (and the more prolonged the administration of antibacterial antibiotics), the greater chance of fungi playing a role in the infection.
8. Recommendations for initial empiric treatment for patients with high-risk febrile neutropenia include broad-spectrum monotherapy with an antipseudomonal β-lactam such as cefepime, a carbapenem, or piperacillin/tazobactam.
9. Parenteral combination therapy can be considered (aminoglycosides, fluoroquinolones, and/or vancomycin), especially for management of complications (e.g., hypotension and pneumonia) or if antimicrobial resistance is expected.
10. Vancomycin is not recommended as standard initial therapy in patients with febrile neutropenia but may be considered for combination therapy with an antipseudomonal β-lactam for the following: sepsis (hemodynamic instability); pneumonia (radiographic evidence); positive blood culture for gram-positive bacteria; catheter-related infection; skin or soft tissue infection; colonization with methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, or penicillin-resistant Streptococcus pneumoniae; or severe mucositis (if fluoroquinolone prophylaxis used).
11. All patients should be reassessed after 3–5 days of antibiotic therapy, and antibiotics should be adjusted accordingly. Empiric antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics whose overall duration of neutropenia is expected to be more than 7 days.
12. Prophylactic antibiotics (fluoroquinolones, trimethoprim/sulfamethoxazole) may be considered for patients who are receiving chemotherapy who are expected to be profoundly neutropenic for more than 7 days.

IV. USE OF COLONY-STIMULATING FACTORS FOR PREVENTION OF FEBRILE NEUTROPENIA

A. CSFs improve both the production and the function of their target cells. Four products and six biosimilars are currently available in the United States: Granulocyte colony-stimulating factor (G-CSF, or filgrastim [Neupogen]) or tbo-filgrastim (Granix), pegylated granulocyte colony-stimulating factor (PEG-G-CSF, pegfilgrastim [Neulasta]) granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]). The biosimilars are filgrastim-sndz (Zarxio), filgrastim-aafi (Nivestym), pegfilgrastim-bmez (Ziextenzo), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-apgf (Nyvepria), and pegfilgrastim-jmdb (Fulphila).

B. Pegfilgrastim, the long-acting agent, and the biosimilars pegfilgrastim-apgf, pegfilgrastim-bmez, pegfilgrastim-cbqv, and pegfilgrastim-jmdb are approved for use in patients with nonmyeloid malignancies who are receiving myelosuppressive chemotherapy associated with a high incidence of febrile neutropenia.

C. Studies have shown that G-CSF and GM-CSF reduce the incidence, magnitude, and duration of neutropenia after chemotherapy and bone marrow transplantation.

D. Guidelines for the use of CSFs were established by the American Society of Clinical Oncology in 1994; the most recent update was published in 2015.

E. CSFs are recommended for primary prophylaxis with chemotherapy regimens associated with a 20% or greater risk of febrile neutropenia.
   1. G-CSF, tbo-filgrastim, GM-CSF, filgrastim-sndz, and filgrastim-aafi are all dosed at 5 mcg/kg and are given by daily subcutaneous injection.
   2. To date, no large trials have compared G-CSF and GM-CSF. Therefore, although it cannot be stated unequivocally that the two are therapeutically equivalent, they are often used interchangeably. However, they have varying adverse effect profiles (increased in fluid retention and fevers with GM-CSF).
   3. A meta-analysis of tbo-filgrastim and filgrastim resulted in tbo-filgrastim being noninferior to filgrastim for reducing the incidence of febrile neutropenia. Toxicities are considered similar between the two agents.
   4. Pegfilgrastim is given as a single 6-mg subcutaneous dose, generally administered 24–72 hours after chemotherapy. Pegfilgrastim on-body injector is also available for administration in the outpatient setting. The on-body single-use injector can be applied on the same day of chemotherapy, but it is designed to deliver the actual dose the next day about 27 hours later. Data are available both for and against same-day dosing of pegfilgrastim, but the dosing schedule with FDA approval (day after chemotherapy) is still recommended.
   5. A single dose of pegfilgrastim is as effective as 11 daily doses of G-CSF 5 mcg/kg in reducing the frequency and duration of severe neutropenia, promoting neutrophil recovery, and reducing the frequency of febrile neutropenia. After a dose of pegfilgrastim is administered, chemotherapy should not be given for 10–14 days.
   6. Tbo-filgrastim was approved in an original biologics license application by the FDA in 2012. The FDA has not approved tbo-filgrastim as a biosimilar to Neupogen (filgrastim).
   7. Filgrastim-sndz was the first biosimilar approved by the FDA (March 2015). Filgrastim-aafi was FDA approved in July 2018 as another biosimilar option to filgrastim.
   8. The choice of CSF (pegfilgrastim vs. filgrastim) should be based on the expected duration of neutropenia and the specific anticancer regimen (e.g., short courses of a daily CSF rather than one dose of pegfilgrastim) with chemotherapy administration on a weekly schedule.
   9. Adverse events associated with all three preparations appear similar; they include bone pain (most common) and fever.
   10. The CSF should be initiated 24–72 hours after the completion of chemotherapy.

11. The package literature recommends continued administration of G-CSF until the post-nadir ANC is greater than 10,000 cells/mm^3; however, both G-CSF and GM-CSF are usually discontinued when adequate neutrophil recovery is evident. To decrease cost without compromising patient outcome, many centers continue the CSF until ANC is greater than 2000–5000 cells/mm^3. Note that the ANC will decrease about 50% per day after the CSF is discontinued if the marrow has not recovered (i.e., if the CSF is discontinued before the ANC nadir is reached).
12. Avoid the concomitant use of CSF in patients receiving chemotherapy and radiation therapy; the potential exists for worsening myelosuppression.

F. See the American Society of Clinical Oncology guidelines for the following indications: increasing chemotherapy dosage intensity, using as adjuncts to progenitor cell transplantation, administering to patients with myeloid malignancies, and using in pediatric populations.

G. American Society of Clinical Oncology Guidelines for Secondary CSF Administration (secondary prophylaxis)
   1. If chemotherapy administration has been delayed or the dosage reduced because of prolonged neutropenia, then CSF use can be considered for subsequent chemotherapy cycles; administering CSF in this setting is considered secondary prophylaxis.
   2. Dosage reduction of chemotherapy should be considered the first option (i.e., instead of a CSF) after an episode of neutropenia in patients being treated with the intent to palliate (i.e., not a curative intent).

H. Use of CSFs for Treatment of Established Neutropenia
   1. Administering CSFs in patients who are neutropenic but not febrile is not recommended.
   2. Administering CSFs in patients who are neutropenic and febrile may be considered in the presence of risk factors for complications (e.g., sepsis syndrome, age older than 65, ANC less than 100 cells/mm^3, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization at time of fever, prior episode of febrile neutropenia); CSFs may be used in addition to antibiotics to treat neutropenia in patients with these risk factors.
   3. Pegfilgrastim is not approved for the treatment of established neutropenia.

Patient Case

Questions 5 and 6 pertain to the following case.

A 50-year-old woman is receiving adjuvant chemotherapy for stage II breast cancer. She received her third cycle of AC (doxorubicin and cyclophosphamide) 10 days ago. Her CBC today includes WBC 600 cells/mm^3, segmented neutrophils 60%, band neutrophils 10%, monocytes 12%, basophils 8%, and eosinophils 10%. She is afebrile.

5. Which best represents this patient's ANC?
   A. 600 cells/mm^3.
   B. 360 cells/mm^3.
   C. 240 cells/mm^3.
   D. 420 cells/mm^3.

6. Given this ANC, which statement is most appropriate?
   A. The patient should be initiated on a CSF.
   B. The patient should begin prophylactic treatment with either a quinolone antibiotic or trimethoprim/sulfamethoxazole.
   C. The patient, who is neutropenic, should be monitored closely for signs and symptoms of infection.
   D. Decrease the dosages of AC with the next cycle of treatment.

V. THROMBOCYTOPENIA

A. Megakaryocytes (platelets) = a normal range of 140,000–440,000 cells/mm^3 with a circulating life span of 5–10 days.

B. Thrombocytopenia is defined as a platelet count less than 100,000 cells/mm^3; however, the risk of bleeding is not substantially elevated until the platelet count is 20,000 cells/mm^3 or less. Practices for platelet transfusion vary widely from institution to institution. Many institutions do not transfuse platelets until the patient becomes symptomatic (ecchymosis, petechiae, hemoptysis, or hematemesis). Other institutions transfuse when the platelet count is 10,000 cells/mm^3 or less, even in the absence of bleeding.

C. Caution should be used in patients receiving antiplatelet therapy. Monitor closely and consider interventions as clinically needed (i.e., holding low-molecular-weight heparin product if platelet count is less than 50,000 cells/mm^3).

VI. ANEMIA AND FATIGUE

A. Overview of Anemia
   1. Occurs in 3.4 million Americans each year and most common in women, African Americans, and older adults
   2. Defined as hemoglobin (Hgb) less than 13 g/dL in men or 12 g/dL in women
   3. Anemia defined as a reduction of RBC mass, number of RBCs, and Hgb concentration of RBCs
   4. Caused by a deficiency, impaired bone marrow function, and peripheral causes.
   5. Signs and symptoms of anemia include weakness and fatigue, irritability, tachycardia and palpitations, shortness of breath, chest pain, pale appearance, dizziness, decreased mental acuity, ecchymoses, blood in urine or stool, and hematomas.
   6. There are several types of anemia, including microcytic (iron deficiency anemia), macrocytic/megaloblastic anemia (vitamin B_{12} deficiency, folic acid deficiency), anemia of chronic disease (including chemotherapy-induced anemia), anemia of critical illness, hemolytic anemias, and drug-induced anemias.
   7. Hematologic laboratory values:

Table 5. Hematologic Laboratory Values

Test	Reference Range	Definition
Hgb	M 13.5–17.5 g/dL F 12–16 g/dL	Hgb per volume of whole blood
Hct	M 41–53% F 36%–46%	Percentage of total blood volume composed of RBCs (3 - Hgb)
MCV	80-96 fL	Average volume of RBCs (Hct/RBC)
MCHC	31%–37%	Weight of Hgb per volume (Hgb/Hct)
MCH	26-34pg	Percentage volume of Hgb in RBC (Hgb/RBC)
RBC	4.5-5.9 million/m^3	RBCs per unit blood
Reticulocyte count	0.5%-1.5%	Immature RBCs
RDW	11%-16%	RBC distribution width
EPO	0-19 mU/mL	Endogenous erythropoietin
Serum iron	M 50-160 mcg/dL F 12-150 mcg/dL	Concentration of iron bound to transferrin Transferrin is a glycoprotein that binds and transports iron in the blood to various tissues throughout the body

Table 5. Hematologic Laboratory Values *(Cont'd)*

Test	Reference Range	Definition
TIBC	250-400 mcg/dL	Iron binding capacity of transferrin
Ferritin	M 15-200 ng/mL F 12-150 ng/mL	Stored iron concentration
Folate	1.8-1.6 ng/mL	Serum folic acid
Vitamin B12	100-900 pg/mL	Serum vitamin B_{12}
Transferrin saturation	>30%	Serum iron divided by TIBC

EPO = erythropoietin; F = female; Hct = hematocrit; Hgb = hemoglobin; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cells; RDW = RBC distribution width; TIBC = iron binding capacity of transferrin.

B. Microcytic Anemia

1. Iron deficiency is the most common nutritional deficiency, with laboratory values reflecting a decreased RBC, Hgb/Hct, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), iron, ferritin, and transferrin. Total iron binding capacity (TIBC) and RBC distribution width (RDW) are increased.
2. Treatment includes oral iron supplementation: 200 mg elemental iron divided twice daily or three times daily for 3–6 months.
3. Available oral iron products (multiple branded agents):

Table 6. Available Oral Iron Products (multiple branded agents)

Product	% Elemental	Elemental Iron (mg)
Ferrous sulfate 325-mg tablet	20	65
Ferrous gluconate 325-mg tablet	12	39
Ferrous fumarate 100-mg tablet	33	33
Polysaccharide iron complex 150-mg capsule	100	150
Carbonyl iron 50 mg caplet	100	50

4. Iron adverse effects include constipation and nausea or vomiting.
5. Iron products should be taken with food to avoid gastrointestinal discomfort (but absorption will be decreased). Vitamin C may increase the absorption of iron and is often used to increase the efficacy of iron products. Iron therapy may cause dark stools.
6. Parental iron products:

Table 7. Parental Iron Products

	Iron Dextran	Sodium Ferric Gluconate	Iron Sucrose	Ferumoxytol	Ferric Carboxymaltose	Ferric Derisomaltose
Elemental iron	50 mg/mL	62.5 mg/5 mL	20 mg/mL	30 mg/mL	50 mg/mL	100 mg/mL
Preservative	None	Benzyl alcohol 9 mg/5 mL 20%	None	None	None	None
Indication	IDA where PO not an option	IDA in patients on chronic HD receiving EPO	IDA in patients on chronic HD receiving EPO	IDA with CKD	IDA with non–dialysis-dependent CKD	IDA with non-dialysis-dependent CKD
Warning	Boxed warning: anaphylactic type reactions	Hypersensitivity reactions	Boxed warning: anaphylactic type reactions	Hypersensitivity reactions	Hypersensitivity reactions	Hypersensitivity reactions; iron overload
IM injection	Yes	No	Yes	No	No	No

Table 7. Parental Iron Products *(Cont'd)*

	Iron Dextran	Sodium Ferric Gluconate	Iron Sucrose	Ferumoxytol	Ferric Carboxymaltose	Ferric Derisomaltose
Usual dosage	100 mg IV push (no faster than 50 mg/min) *Large single-dose (1000 mg) infusions have been used in clinical practice	125 mg diluted in 100 ml NS over 60 min (IV injection at 12.5 mg/min)	100 mg at 1 mL undiluted solution/ min into dialysis line *Larger doses have been used off-label for convenience	510 mg IV injection repeated 3–8 days later	750 mg IV injection repeated 7 days later or 1000 mg IV injection as a single dose	1000 mg IV injection × 1 dose
Test dose	Yes	No	No	No	No	No
Common adverse events	Pain, stinging at injection site, local discoloration at injection site, hypotension, flushing, chills, fever, myalgia, anaphylaxis	Cramps, nausea or vomiting, flushing, hypotension, rash, pruritus	Leg cramps and hypotension	Diarrhea, constipation, nausea, dizziness, hypotension, peripheral edema	Hypophosphatemia, dizziness, nausea	Hypophosphatemia, nausea, rash

CKD = chronic kidney disease; EPO = erythropoietin; HD = hemodialysis; IDA = iron deficiency anemia; IM = intramuscular; IV = intravenous; NS = normal saline; PO = by mouth.

C. Macrocytic Anemia
   1. Vitamin B_{12} and folate deficiency are the most common causes of macrocytic anemia. Causes of B_{12} deficiency include inadequate intake, malabsorption, and inadequate utilization. Folate deficiency is caused by inadequate intake, decreased absorption, hyperutilization, and inadequate utilization.
   2. In B_{12} deficiency RBC, Hgb and Hct, and serum B_{12} are decreased, with an increase in MCV, MCH, methylmalonic acid, and homocysteine. Hypersegmented polymorphonuclear leukocytes may also be present on the peripheral smear.
   3. In folate deficiency, RBC, Hgb and Hct, and serum folic acid are decreased, with an increase in MCV and MCH. B_{12} will be normal (will need to rule out this deficiency).
   4. In B_{12} deficiency, patients may experience neurological changes, glossitis, weakness, loss of appetite, and possibly thrombocytopenia, leucopenia, and pancytopenia. Folate deficiency also presents with glossitis and other central nervous system symptoms including weakness, forgetfulness, headache, syncope, and loss of appetite.
   5. Treatment options for vitamin B_{12} deficiency include oral replacement daily or intramuscular replacement weekly for 1 month, then monthly.
   6. Folate deficiency anemia should be treated with 1 mg of folate daily for 4 months. Pregnant women should take supplements to prevent neural tube defects in the fetus.

D. Anemia of Chronic Disease (Specifically Chemotherapy-Induced Anemia): Causes of Anemia and Fatigue in Adult Patients with Cancer
   1. Unmanaged pain or other symptoms can increase fatigue.
   2. Decreased RBC production because of anticancer therapy, either radiation or chemotherapy
   3. Decreased or inappropriate endogenous erythropoietin production or decreased responsiveness to endogenous erythropoietin
   4. Decreased body stores of vitamin B_{12}, iron, or folic acid
   5. Increased destruction of RBCs
   6. Blood loss
   7. Although anemia can certainly contribute to or worsen fatigue, there are probably other (perhaps many) mechanisms of fatigue (e.g., cytokines) that are independent of Hgb concentration.

E. Principles of Anemia and Fatigue
   1. Fatigue is estimated to affect 60%–80% of all patients with cancer.
   2. Fatigue may be caused by the disease or treatment.
   3. Fatigue can be assessed with a numeric rating scale, 0 = no fatigue and 10 = worst fatigue imaginable, or with any of several questionnaires (e.g., FACT-An).
   4. Drugs used in the treatment of anemia and fatigue
      a. Epoetin and darbepoetin alfa (erythropoiesis-stimulating agents [ESAs]) are approved for treating chemotherapy-induced anemia, the end point of treatment being a decreased need for transfusion. Darbepoetin has additional carboxy chains, resulting in a longer half-life compared with epoetin.
      b. In May 2018, the FDA approved the first biosimilar for the treatment of anemia, epoetin alfa-epbx, for all indications of the originator product. This biosimilar has been studied in patients with chronic kidney disease, but data are limited in patients with cancer. However, a related biosimilar, epoetin zeta, has been approved for use as a biosimilar in Europe since 2007.
      c. Reports of a detrimental effect of ESAs (e.g., increased deaths, reduced chemotherapy outcomes) have led to changes in practice guidelines and reimbursement for these agents. Hgb targets are lower than they were previously, and Hgb is carefully monitored. According to the most recent guidelines, ESAs are initiated once a patient's Hgb drops below 10 g/dL.
      d. It is important to distinguish between the use of these agents for chemotherapy-associated anemia and cancer-associated anemia. The latter is not an approved use. These agents should be used only in the noncurative setting.
      e. Adverse events: Hypertension and seizures, venous thromboembolism, and pure red cell aplasia (rare)
      f. The use of these agents requires baseline and follow-up monitoring to determine whether agents need titration or discontinuation.
   5. Transfusions are an option if patients are symptomatic. Transfusion goal is to maintain Hgb at 8–10 g/dL. When considering RBC transfusion, see the AABB 2016 clinical practice guidelines.

F. Dosing of Erythropoiesis-Stimulating Agents

Table 8. Dosing of Erythropoiesis-Stimulating Agents

Agent	Starting Dosage	Dosage Increase	Dosing Parameters
Epoetin alfa or epoetin alfa-epbx (Procrit, Epogen, Retacrit [biosimilar])	150 units/kg subcutaneously 3 times/wk 40,000 units subcutaneously weekly	300 units/kg subcutaneously 3 times/wk 60,000 units subcutaneously weekly	Hgb must be < 10 to initiate and continue therapy Evaluate after 4 wk and increase dosage if rise is < 1 g/dL Decrease by ~25% if rapid rise in Hgb Discontinue therapy if no response after 8 wk
Darbepoetin (Aranesp)	2.25 mcg/kg subcutaneously weekly 500 mcg every 3 wk	4.5 mcg/kg subcutaneously weekly Not applicable	Hgb must be < 10 to initiate and continue therapy Evaluate after 6 wk and increase dosage if rise is < 1 g/dL Decrease by ~40% if rapid rise in Hgb Discontinue therapy if no response after 8 wk

G. REMS for ESAs
   1. Historically the FDA required these agents to be prescribed and monitored under a risk management program to ensure their safety.
   2. In 2017, the FDA determined that the ESA REMS, which was limited to the use of erythropoietin (Procrit, Epogen) and darbepoetin (Aranesp) to treat patients with anemia caused by chemotherapy, is no longer required.

3. Although the ESA REMS may no longer be required, clinicians should keep these risks in mind and continue to discuss the risk-benefit of using ESAs with each patient before initiating therapy.

Patient Case

7. A 45-year-old woman is beginning her third cycle of chemotherapy for the adjuvant treatment of breast cancer. At diagnosis, her Hgb was 10 g/dL; however, today, it is less than 10 g/dL. The patient has fatigue that is interfering with her activities of daily living. Which is the most appropriate treatment option?
   A. Treatment with epoetin should be considered.
   B. Treatment with darbepoetin should be considered when Hgb decreases to less than 9 g/dL.
   C. The patient is being treated in the curative setting and therefore is not eligible to receive an ESA.
   D. The patient should not receive RBC transfusions because she is symptomatic.

VII. CHEMOPROTECTANTS

A. Properties of an Ideal Protectant Drug for Chemotherapy- and Radiation-Induced Toxicities
   1. Easy to administer
   2. No adverse events
   3. Prevents all toxicities, including non–life-threatening (e.g., alopecia) toxicities, irreversible morbidities (e.g., neuropathies, ototoxicity), and mortality (e.g., severe myelosuppression, cardiotoxicity)
   4. Does not interfere with the efficacy of the cancer treatment
   5. To date, no such drug has been identified.

B. Dexrazoxane
   1. The anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) and anthracenedione (i.e., mitoxantrone) can cause cardiomyopathy that is related to the total lifetime cumulative dosage.
   2. Dexrazoxane acts as an intracellular chelating agent; iron chelation leads to a decrease in anthracycline-induced free radical damage.
      a. Dexrazoxane may be considered for patients who have received doxorubicin 300 mg/m^2 or more and who may benefit from continued doxorubicin, considering the patient's risk of cardiotoxicity with continued doxorubicin use.
      b. Dexrazoxane is dosed in relation to doxorubicin at a ratio of 10:1 dexrazoxane to doxorubicin dose.
      c. Dexrazoxane may increase the hematologic toxicity of chemotherapy at high doses (greater than 750 mg).
      d. An early study suggested that dexrazoxane decreases the response rate to chemotherapy. More recent data suggest this is not the case, but dexrazoxane is still not indicated for patients with early (curable) breast cancer.
   3. Dexrazoxane is also approved for use as an antidote for the extravasation of anthracycline chemotherapy.

C. Amifostine
   1. Amifostine is used to prevent nephrotoxicity from cisplatin.
   2. It is also used to decrease the incidence of both acute and late xerostomia in patients with head and neck cancer who are undergoing fractionated radiation therapy.
   3. Adverse events associated with amifostine include sneezing, allergic reactions, warm or flushed feeling, metallic taste in mouth during infusion, nausea and vomiting, and hypotension. The latter two are the most clinically significant toxicities. Prevention of hypotension includes withholding antihypertensive medications, using hydration, and close blood pressure monitoring. Because of the problems with nausea and vomiting (30%–60%) and the incidence of hypotension, this agent is not often used in clinical practice.

D. Mesna (sodium-2-mercaptoethane sulfonate)
   1. The metabolite acrolein is produced from metabolism of both cyclophosphamide and ifosfamide, and it has been implicated in sterile hemorrhagic cystitis.
   2. Mesna inactivates acrolein by binding to the urotoxic metabolite and preventing its interaction with host cells in the bladder.
   3. Mesna is always used with ifosfamide and may be used with cyclophosphamide (in dosages of 1500 mg/m^2 or greater), although this is not a label indication.
   4. Mesna may be given intravenously or orally and is usually 60%-100% of the ifosfamide dose. The oral dose is twice the parenteral dose. Several dosing schedules may be used. With any schedule, mesna must begin concurrently with or before ifosfamide or cyclophosphamide and end after ifosfamide or cyclophosphamide because of its short half-life (i.e., mesna must be present in the bladder when acrolein is present in the bladder).

E. Leucovorin
   1. Leucovorin rescue may be used after methotrexate doses greater than 100 mg/m2; in general, methotrexate doses greater than 500 mg/m2 require leucovorin rescue.
   2. Factors that increase the likelihood of methotrexate toxicity include renal dysfunction (causing delayed elimination), third-space fluid (e.g., pleural effusion, ascites), and administration of other drugs that may delay methotrexate (pump inhibitors). Toxic reactions include mucous membrane toxicity (e.g., oral mucositis), renal and hepatic toxicity, central nervous system toxicity, and myelosuppression.
   3. The dosage of leucovorin depends on the methotrexate dosage or concentration and the time since completing methotrexate. Methotrexate concentrations are usually obtained 24–48 hours after intermediate-or high-dose methotrexate, and leucovorin is continued until the methotrexate concentration decreases to less than 0.1 mM (less than $1 \times 10\text{-}7$ M). This regimen is typically protocol driven.
   4. In contrast with its use with methotrexate, leucovorin is given in combination with fluorouracil in colorectal cancer to improve activity, not to rescue normal cells

F. Glucarpidase
   1. Glucarpidase, a carboxypeptidase enzyme, is now approved and indicated for treating toxic methotrexate concentrations (greater than 1 micromole/L) in patients with delayed methotrexate clearance because of renal dysfunction.
   2. Administered as a single intravenous dose of 50 units/kg.
   3. Continue leucovorin until the methotrexate concentration has been maintained below the leucovorin treatment threshold for at least 3 days. However, caution must be used with administering leucovorin in conjunction with glucarpidase.
   4. Leucovorin should not be administered within 2 hours before or after a dose of glucarpidase because glucarpidase can decrease leucovorin concentrations. Both are used to prevent methotrexate toxicities, so proper timing of administration is key.

G. Trilaciclib
   1. Approved to decrease the incidence of chemotherapy-induced myelosuppression prior to platinum/etoposide regimens or topotecan-containing regimens for small cell lung cancer.
   2. Trilaciclib is an inhibitor of cyclin-dependent kinase 4/6, on which hematopoietic stem cells and progenitor cells in the bone marrow depend to produce neutrophils, red blood cells, and platelets.
   3. Administered at the dose of 240 mg/m^2 as a 30-minute intravenous infusion that must be completed within 4 hours before the start of chemotherapy on each day chemotherapy is administered.

Patient Cases

8. A 38-year-old woman has a history of Hodgkin lymphoma. Two years ago, she completed six cycles of ABVD chemotherapy (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine). Each cycle included doxorubicin 50 mg/m^2. Recently, she was given a diagnosis of stage IV breast cancer. She will be initiated on doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 for four cycles. Which statement is most applicable?
   A. The patient has not reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane.
   B. The patient has reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane
   C. The patient should not receive any more doxorubicin because she is at an elevated risk of cardiotoxicity.
   D. The patient should not receive dexrazoxane because of the possibility of increased myelosuppression.

9. Which is the best sequence for administering mesna and ifosfamide?
   A. Mesna before ifosfamide and then at 4 and 8 hours after ifosfamide.
   B. Ifosfamide before mesna and then at 4 and 8 hours after mesna.
   C. Mesna and ifosfamide beginning and ending at the same time.
   D. Mesna on day 1 and ifosfamide on days 2–5.

VIII. ONCOLOGIC EMERGENCIES

A. Hypercalcemia
   1. The most common tumors associated with hypercalcemia are lung (metastatic non–small cell lung cancer more than small cell lung cancer), breast, multiple myeloma, head and neck, renal cell, and non-Hodgkin lymphoma.
   2. Cancer-associated hypercalcemia results from increased bone resorption with calcium release into the extracellular fluid; in addition, renal clearance of calcium is decreased.
      a. Some tumors cause direct bone destruction, resulting in osteolytic hypercalcemia.
      b. Other tumors release parathyroid hormone–related protein (i.e., humoral hypercalcemia).
      c. Immobile patients are also at an elevated risk of hypercalcemia because of increased resorption of calcium.
      d. Medications (e.g., hormonal therapy, thiazide diuretics) may precipitate or exacerbate hypercalcemia.
      e. Corrected Ca (mg/dL) = (4 – plasma albumin in g/dL) × 0.8 + serum calcium.
      f. Symptoms of hypercalcemia: Lethargy, confusion, anorexia, nausea, constipation, polyuria, and polydipsia
   3. Management of hypercalcemia
      a. Mild hypercalcemia (corrected calcium less than 12 mg/dL) may not warrant aggressive treatment. Hydration with normal saline followed by observation is an option in asymptomatic patients with chemotherapy-sensitive tumors (e.g., lymphoma, breast cancer).
      b. Moderate hypercalcemia (corrected calcium 12–14 mg/dL) requires basic treatment of clinical symptoms with aggressive hydration.
      c. Severe hypercalcemia (corrected calcium greater than 14 mg/dL; symptomatic) requires aggressive inpatient treatment.
         i. Hydration with normal saline about 3–6 L in 24 hours
         ii. Loop diuretics may be administered after volume status has been corrected or to prevent fluid overload during hydration.
         iii. Thiazide diuretics are contraindicated in hypercalcemia because of the increase in renal tubular calcium absorption.

iv. Bisphosphonates bind to hydroxyapatite in calcified bone, which prevents dissolution by phosphatases and inhibits both normal and abnormal bone resorption. The onset of action is 3–4 days.
v. Calcitonin (intramuscular formulation) inhibits the effects of parathyroid hormone and has a rapid-onset (though short-lived) hypocalcemic effect. May cause tachyphylaxis
vi. Steroids may be used to lower calcium in patients with steroid-responsive tumors (lymphoma and myeloma).
vii. Phosphate is reserved for patients who are both hypophosphatemic and hypercalcemic. Phosphate is seldom used because of the possibility of calcium and phosphate precipitation in soft tissue.
viii. Dialysis may be needed in patients with hypercalcemia and renal failure.

B. Spinal Cord Compression
1. Signs and symptoms include back pain, weakness, paresthesias, and loss of bowel and bladder function.
2. Treatment consists of dexamethasone and radiation therapy or surgery.

C. Tumor Lysis Syndrome
1. Occurs secondary to the rapid cell death that follows the administration of chemotherapy in patients with leukemia or lymphoma or in patients with high tumor burdens from other diseases that are also highly chemosensitive. Tumor lysis syndrome (TLS) can occur spontaneously in hematologic malignancies, without being triggered by the administration of chemotherapy (i.e., some patients present in tumor lysis).
2. Manifestations include hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia. Uric acid and calcium/phosphorus may precipitate in the kidney and can lead to renal failure.
3. The primary management strategy is prevention with parenteral hydration (with normal saline) and allopurinol.
4. Rasburicase is a recombinant urate oxidase that converts uric acid into allantoin, which is 5–10 times more soluble in urine than uric acid. Rasburicase should be considered for patients at high risk of developing TLS, such as those with a serum uric acid concentration greater than 8 mg/dL, a large tumor burden, preexisting renal dysfunction, or an inability to take allopurinol. The drug is expensive, and currently it is not recommended for prophylaxis in all patients but may be used together with hydration for treatment of TLS. The approved dosage is 0.2 mg/kg intravenously for five doses. There is now increasing evidence for the use of an off-label, low, fixed, single dose (3–6 mg) of rasburicase for chemotherapy-induced hyperuricemia in adults. The FDA indication is management of uric acid concentrations. Rasburicase causes enzymatic degradation of the uric acid in blood, plasma, and serum samples, potentially resulting in spuriously low plasma uric acid assay readings. Blood must be collected in pre-chilled tubes containing heparin anticoagulant; immediately immerse plasma samples for uric acid measurement in an ice water bath.

IX. MISCELLANEOUS ANTINEOPLASTIC PHARMACOTHERAPY

A. Extravasation Injuries
1. A vesicant is an agent that, on extravasation, can cause tissue necrosis. Vesicant antineoplastic drugs include doxorubicin, daunorubicin, epirubicin, mechlorethamine, mitomycin, vincristine, vinblastine, vinorelbine, and streptozocin.
2. Anthracyclines cause the most severe tissue damage on extravasation.

3. The literature generally recommends administering vesicants by parenteral injection rather than infusion, but some exceptions exist.
    a. Some institutional policies require infusions for every drug or approved protocols.
    b. Vincristine has been incorrectly administered by intrathecal injection, with fatal consequences. Dilution of vincristine for administration as a short parenteral infusion has been recommended to prevent this error from occurring.
    c. Paclitaxel (an irritant with vesicant-like properties) is administered as an infusion (1, 3, or 24 hours, depending on the protocol).
4. Management of extravasation
    a. Cold for doxorubicin, daunorubicin, and epirubicin
    b. Heat for vincristine, vinblastine, and vinorelbine
    c. Sodium thiosulfate for mechlorethamine
    d. Topical dimethyl sulfoxide has been recommended for anthracyclines. Its use is not as well established as that of the antidotes given earlier. Hyaluronidase is recommended for vinca alkaloids, but hyaluronidase is of limited availability. Antidotes for mitomycin, streptozocin, paclitaxel, and oxaliplatin are not well documented in the literature.
    e. Dexrazoxane (Totect) for doxorubicin, daunorubicin, idarubicin, and epirubicin. Cold compress should be removed 15 minutes before dexrazoxane treatment.
    f. Many institutions do not allow the administration of vesicants through a peripheral vein but instead require that vesicants be administered through a central line with a venous access device. Although administering vesicants through a central line minimizes the likelihood of an extravasation injury, extravasation may still occur. Management of extravasation is intended for suspected or actual extravasation from a peripheral or central vein.

B. Management of Diarrhea
1. Intensive loperamide therapy using dosages higher than recommended is sometimes necessary for irinotecan-induced diarrhea. Atropine is used to prevent cholinergic activity of acute irinotecan-induced diarrhea (given during administration of chemotherapy). There is no maximal dosage of loperamide when used for delayed diarrhea in this setting (greater than 24 hours after irinotecan administration). The recommended dosing regimen of loperamide is 4 mg by mouth, followed by 2 mg every 2 hours until diarrhea free.
2. Intensive antidiarrhea treatment is also used for other agents (e.g., fluorouracil, epidermal growth factor receptor inhibitors).
3. Diarrhea/colitis caused by immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab) may require steroid treatment to resolve symptoms.

C. Dosage Adjustment for Organ Dysfunction
1. Conflicting recommendations for dosage adjustment have been reported. Many drugs have not been studied in patients with organ dysfunction. Consultation of oncology-specific drug information resources may be useful.
2. Dosage adjustment for renal dysfunction may be considered for methotrexate, carboplatin, cisplatin, etoposide, bleomycin, topotecan, capecitabine, and lenalidomide.
3. Dosage adjustment for hepatic dysfunction is often based on total bilirubin concentrations and may be considered for anthracyclines, vinca alkaloids, taxanes, methotrexate, and other agents.

D. Immunotherapy-Related Toxicities
1. There is a dynamic relationship between the immune system and cancer cells. Immune cells can detect genetic and cellular abnormalities located on cancer cells. The immune system has several mechanisms in place to regulate its activation and function.

2. However, malignant cells can also manipulate the activity of immune cells, allowing cancer cells to evade recognition and destruction by the immune system.
3. New breakthroughs in immunotherapy have led to many FDA approvals and treatment changes across various malignancies. These treatment developments include immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy, as well as bispecific antibody therapies..
4. Some of the most effective immunotherapies to date focus on targeting immune checkpoints that are exploited by cancers to decrease immune activity. Immune checkpoint proteins such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are closely regulated by immune cells to modulate T-cell activity. Cancer cells can disrupt various immune mechanisms, including immune checkpoints, to evade recognition by the immune system.
5. CTLA-4 and PD-1/PD-L1 inhibitors lead to the reactivation of T-cell populations inhibited by antitumor cells, allowing for immune response against cancer cells.
    a. CTLA-4 is expressed by CD4+ (helper), DC8+ (cytotoxic), and regulatory T cells and functions as an early inhibitory signal during the priming phase. CTLA-4 blockade results in more effector T-cell clones activating and proliferating while reducing the immunosuppressive activity of regulatory T cells.
    b. Ipilimumab is a CTLA-4 agent approved for various cancer types as monotherapy and in combination with the PD-1 inhibitor nivolumab.
    c. PD-1 receptor is present on various immune cells such as T cells, B cells, and natural killer cells. The ligands of PD-1 (PD-L1 and PD-L2) are expressed in a wide variety of tissue types. PD-L1 is commonly expressed on tumor cells, allowing for possible drug targets. PD-L2 is mainly expressed on hematopoietic cells.
    d. Currently available PD-1 inhibitors include cemiplimab-rwlc, dostarlimab-gxly, nivolumab, and pembrolizumab.
    e. Currently available PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab.
6. Because of the mechanism of immune checkpoint inhibitors, various toxicities may arise from these agents, including immune-related adverse events (irAEs). These toxicities may have an early or late onset and result from various distinct mechanisms that are not yet fully understood. One potential mechanism is T-cell activity directed at antigens present on both tumor cells and healthy tissue, leading to toxicity.
    a. Immune-related toxicities to monitor patients for include the following: diarrhea/colitis, fatigue, hepatitis, hypophysitis, thyroid disorders (hypo/hyperthyroidism), pneumonitis, myocarditis, nephritis, uveitis, and dermatitis.
    b. Patients should be monitored closely for irAEs and counseled on signs and symptoms of these toxicities.
    c. ASCO and NCCN have developed guidelines for the management of immune checkpoint inhibitor toxicities.
    d. General treatment recommendations for moderate to severe (grade 2–4) irAEs involve holding immunotherapy and initiating high-dose corticosteroid treatment with prednisone/methylprednisolone (1–2 mg/kg/day). Severe toxicity management may require inpatient admission and treatment with intravenous corticosteroids. Thyroid disorders are an exception and are not typically treated with corticosteroids. Instead, thyroid replacement therapy is used for hypothyroidism, and supportive care management is used for thyrotoxicosis. Thyrotoxicosis often evolves to hypothyroidism requiring thyroid replacement therapy (50%–90%).
    e. If patients have irAEs that are refractory to high-dose corticosteroid treatment (i.e., no improvement in 1–2 days), other immunosuppressive therapies such as infliximab can be used. Vedolizumab may be considered in patients whose disease is refractory to infliximab and/or for tumor necrosis factor (TNF) alpha blockers such as infliximab are contraindicated. Mycophenolate mofetil should be used for corticosteroid-refractory hepatitis instead of infliximab because of the potential risk of idiosyncratic liver failure with infliximab.

7. CAR T-cell adverse reactions
    a. Cytokine release syndrome (CRS) is a complication related to CAR T-cell administration that occurs in over 50% of patients receiving therapy. CRS results from a massive release of various cytokines (including interleukin [IL]-6, interferon, and TNF). Typical onset is after 2–3 days and typical duration is 7–8 days. Symptoms range from mild to severe and include flu-like symptoms, fever, fatigue, rash, nausea/vomiting, hypoxemia, and hypotension. Treatment involves symptom management, supportive care, and IL-6 inhibitors such as tocilizumab. Corticosteroids can be added to tocilizumab therapy for higher-grade CRS.
    b. Immune effector cell–associated neurotoxicity syndrome (ICANS) is another complication related to CAR T-cell therapy that occurs in around 30%–50% of patients. Typical time to onset is 4–10 days and typical duration is 14–17 days. Symptoms range from mild to severe and include seizure, encephalopathy, and cerebral edema. Management includes supportive care and intravenous fluids, corticosteroids, anti–IL-6 therapy (tocilizumab), and seizure management.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This highly emetogenic regimen is associated with delayed nausea and vomiting. The best choice is a serotonin receptor antagonist with dexamethasone and aprepitant for prophylaxis against nausea and vomiting per NCCN guidelines (Answer A is correct). Prochlorperazine is not effective against a highly emetogenic stimulus (Answer B is not correct). Granisetron and ondansetron are both serotonin receptor antagonists, and no rationale exists for combining them (Answer C is not correct). Lorazepam may be a useful addition, but the combination of ondansetron and metoclopramide is not recommended per NCCN guidelines (Answer D is not correct).

2. Answer: D

Lorazepam is recommended for use in combination with the standard antiemetic regimen based on chemotherapy emetogenicity to prevent anticipatory nausea and vomiting (Answer D is correct). Aprepitant plus palonosetron plus dexamethasone alone has no effects on anticipatory nausea/vomiting, but the combination can be useful for acute and delayed nausea/vomiting (Answer A is not correct). The aprepitant plus prochlorperazine plus dexamethasone regimen does not provide any additional benefit to treat the sensory symptoms (Answer B is not correct). Metoclopramide added to an aprepitant/granisetron regimen would not be appropriate for anticipatory nausea and vomiting (Answer C is not correct).

3. Answer: D

The patient is taking oxycodone/acetaminophen 5 mg/325 mg, which provides 60 mg of oxycodone per day and 3900 mg of acetaminophen. His current drugs should not be increased because of concerns about acetaminophen toxicity. If he were changed to a higher strength of the combination product, acetaminophen toxicity would still be a concern, which eliminates the choices of increasing to oxycodone/acetaminophen the dose to 7.5mg or 10mg (Answer A and B are not correct). Adding sustained-release morphine is a good option and continuing ibuprofen might be helpful for bone pain (Answer D is correct, Answer C is not correct). Oxycodone/acetaminophen, which is short acting, could be continued for breakthrough pain, but he is already receiving high dosages of acetaminophen without good pain relief.

4. Answer: C

Gabapentin might help the neuropathic component (i.e., the shooting pains) of his pain (Answer C is correct). He is already receiving an NSAID, so there is no need to add naproxen (Answer A is not correct). There is no reason to add acetaminophen as it will not provide additional benefit (Answer B). The case does not mention muscle spasms and therefore Baclofen will likely not be effective (Answer D is not correct).

5. Answer: D

To calculate the ANC, multiply the WBC by the segmented neutrophils and the band neutrophils: 600 cells/mm^3 × (0.6 + 0.1) = 420 cells/mm^3 (Answer D is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, B, and C are not correct)

6. Answer: C

The patient is neutropenic; however, she should not begin a CSF. Her ANC is greater than 100 cells/mm^3, and she has no signs or symptoms of active infection (Answer A is not correct). Prophylactic treatment with antibiotic drugs is not necessary and can increase the risk of resistant organisms (Answer B is not correct). At this time, the patient should be monitored for evidence of infection (e.g., she should be instructed to take her temperature and return to the clinic or emergency department if she has a single oral temperature of 101°F or more or of 100.4°F or more for at least 1 hour or if she develops any signs or symptoms of infection) (Answer C is correct). Because the disease is potentially curable, dosages should not be reduced on the next cycle (Answer D is not correct).

7. Answer: C

Recent literature and subsequent changes in guidelines and Centers for Medicare & Medicaid Services reimbursement suggest that an erythropoiesis-stimulating protein should be considered when Hgb is less than 10 g/dL. However, this patient is being treated potentially for a cure; therefore, she would not be eligible for an ESA (Answer A and B are not correct, Answer C is correct). Transfusions are an option if patients are symptomatic (Answer D is not correct). The transfusion goal is to maintain Hgb at 8–10 g/dL.

8. Answer: B

The patient has received a cumulative dose of 300 mg/m^2 of doxorubicin (50 mg/m^2 × 6 cycles). This is the appropriate cumulative dosage of doxorubicin for dexrazoxane to be considered (Answer A is not correct, Answer B is correct). She is at an elevated risk of cardiotoxicity; however, dexrazoxane protects the heart from this toxicity (Answer C is not correct). Dexrazoxane may increase the myelosuppression from chemotherapy, but that does not represent a contraindication (Answer D is not correct).

9. Answer: A

Several different schedules of ifosfamide and mesna administration exist (e.g., ifosfamide short infusion, followed by intermittent infusions of mesna and continuous infusion of both ifosfamide and mesna). Most schedules recommend the administration of mesna prior to ifosofamide to prevent hemorrhagic cystitis (Answer A is correct, Answer B is not correct). Mesna should always be continued longer than ifosfamide (Answer C and D are not correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

According to the NCCN guidelines, this regimen would likely be considered highly emetogenic. According to these guidelines, an NK1-based regimen with a serotonin-3 antagonist and dexamethasone combination would be recommended (Answer C is correct). However, the patient is likely having some anticipatory nausea/vomiting. Patients who have had poor control of nausea and vomiting on previous cycles of chemotherapy are at an elevated risk of anticipatory emesis. Anxious patients are also at an elevated risk of CINV. Benzodiazepines help decrease anxiety and, by causing anterograde amnesia, may minimize anticipatory symptoms (Answer C is correct). Although it is unclear whether patients who do not respond to one serotonin receptor antagonist will respond to another, a change in regimen is needed (Answer A is not correct). Substituting dolasetron for granisetron would be acceptable, but adding lorazepam is essential (Answer B is not correct). Metoclopramide is another option, but an effective dose might be difficult to administer orally (especially as tablets), and again, adding lorazepam would be preferred to adding aprepitant in this patient(Answer D is not correct).

2. Answer: D

The corrected calcium is 13.6 mg/dL. Corrected calcium concentrations greater than 12 g/dL should be treated with a bisphosphonate (either pamidronate or zoledronic acid) in addition to hydration with normal saline(Answer D is correct). Furosemide may be needed during hydration, but not before hydration because the patient is probably dehydrated (Answer B is not correct). This patient does not need rapid reversal of hypercalcemia; therefore, calcitonin is not needed (Answer A is not correct). Dexamethasone may be used in patients with lymphoma or myeloma, but it has no effect on metastatic non–small cell lung cancer (Answer C is not correct).

3. Answer: C

The patient is at risk of TLS because he has a chemosensitive tumor and a high tumor burden (elevated WBC). Prevention is key in TLS, which includes adequate saline hydration and the use of allopurinol (Answer C is correct). Dextrose 5% is an inappropriate parenteral fluid for hydration because it does not contain saline (Answer A and B are not correct). The value of alkalinization with sodium bicarbonate is somewhat controversial, but alkalinization is not a replacement for allopurinol (Answer D is not correct).

4. Answer: B

This anemia is not attributable to treatment because chemotherapy has not yet begun. Epoetin and darbepoetin are indicated only for noncurative chemotherapy-associated anemia in non-myeloid tumors (answer A is not correct). Chemotherapy should not be delayed, nor should chemotherapy dosages be reduced in the setting of a potentially curable malignancy (Answer C and D are not correct). Therefore, the patient should receive a transfusion of packed RBCs because his hemoglobin is less than 8 g/dL and he is fatigued (Answer B is correct).

5. Answer: B

(55% segmented neutrophils + 5% band neutrophils) × 500 = 300 cells/mm^3 (Answer B is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, C and D are not correct)

6. Answer: A

The patient is neutropenic (ANC 300 cells/mm^3). A temperature of 103°F places the febrile neutropenia outside the definition of low-risk febrile neutropenia (Answer B is not correct). Therefore, the patient should be hospitalized for parenteral antibiotics and an infection workup (Answer A is correct). She has none of the appropriate reasons to administer CSFs (i.e., documented pneumonia, hypotension, sepsis syndrome, or fungal infection) (answer C is not correct). Her chemotherapy may need to be delayed, but it should be continued on count recovery (Answer D is not correct). She should receive a CSF with the next cycle of chemotherapy.

7. Answer: B

In this patient, febrile neutropenia developed at the time of the expected neutrophil nadir, 12 days after chemotherapy (Answer B is correct). Marrow recovery would be expected to follow (Answer A is not correct). The percentage of eosinophils may be slightly elevated, but the absolute count is low (Answer C is not correct). The platelet count is also low, not elevated. Neutrophils

are often affected by myelosuppressive chemotherapy to a greater degree than are platelets (Answer D is not correct).

8. Answer: D
Opioids may provide some relief from neuropathic pain, but often, the response to opioids is less than optimal. In general, higher opioid dosages provide greater pain relief; therefore, increasing the dosage of fentanyl and morphine is an option for this patient but will likely not be effective because of the descriptions of neuropathic pain (Answer B is not correct). Adjuvant analgesic drugs, including tricyclic antidepressants and anticonvulsants, are used to help manage neuropathic pain. Gabapentin, with a good adverse event profile, is a reasonable option. However, adjuvant analgesic drugs should not be given to decrease the opioid dosage or discontinue the use of opioid drugs (Answer A is not correct). Adding gabapentin to the current medication profile is the best choice (Answer D is correct). It may be possible to decrease the dosages of opioids later if gabapentin provides adequate pain relief. Diazepam is more effective for muscle spasms than for neuropathic pain, and this option includes decreasing the fentanyl dosage at the same time as the new drug is initiated (Answer C is not correct).

9. Answer: D
Limited-stage small cell lung cancer is potentially curable; therefore, the patient should continue on the planned chemotherapy dosages. The correct dosage of filgrastim is 5 mcg/kg/day subcutaneously, not 250 mcg/m^2 (this is the dose for sargramostim) (Answer A is not correct) . The correct dosage for pegfilgrastim is a single 6-mg injection (Answer C is not correct). Filgrastim should not be given on the same day as chemotherapy (Answer B is not correct, Answer D is correct).

10. Answer: A
Doxorubicin undergoes hepatic clearance (by the biliary tract), and there are recommendations for dosage reduction based on bilirubin (Answer A is correct). There is no reason to reduce the cyclophosphamide dosage (Answer B is not correct). Because only doxorubicin requires reduction, both agents should not be adjusted based on the laboratory values given (Answer D is not correct). Both agents shouldn't be continued at the current dose as doxorubicin must be adjusted in patients with elevated total bilirubin (Answer D is not correct).

11. Answer: A
Large cell lymphoma is faster growing and more chemosensitive than metastatic colorectal cancer (Answer B is not correct). Therefore, patients with large cell lymphoma are more likely to develop hyperuricemia or TLS from rapid cell turnover, both before treatment and after chemotherapy (Answer A is correct). Hypercalcemia is not a common complication of either of these diseases. Some aggressive lymphomas may be associated with hypercalcemia, but pamidronate is used to treat, not prevent, this complication (Answer C and D are not correct).

12. Answer: C
Neither patient should undergo chemotherapy with an ANC of 800 cells/mm^3(Answer A and B are not correct). Both can be treated when neutropenia resolves (probably within 1 week). It is important to keep patient 1 on schedule because his disease is potentially curable; therefore, patient 1 should receive filgrastim after the next chemotherapy treatment to prevent another dose delay (answer C is correct). When patient 2 resumes chemotherapy, his dosages can be decreased to prevent a recurrence of neutropenia (Answer D is not correct).

13. Answer: C
Injury after extravasation of an anthracycline is potentially the most severe. Therefore, when the recommended antidotes for different vesicants conflict (e.g., heat vs. cold), treatment should be directed at the anthracycline (Answer B is not correct). Dexrazoxane is now indicated for doxorubicin extravasation (Answer C is correct). Cold, rather than heat, would also be appropriate (Answer A is not correct). Although vincristine is considered a vesicant, sodium thiosulfate is not the recommended antidote (Answer D is not correct).

14. Answer: A
Immune-related toxicities can occur with immunotherapy such as PD-1/PD-L1 and CTLA-4 inhibitors and are more common with combination therapy such as nivolumab and ipilimumab. This patient has grade 3 colitis related to immune checkpoint inhibitor therapy. The patient has reported 8 loose stools per day and is dehydrated. Because this is a severe irAE, the patient should be admitted to the hospital for fluid management and high-dose intravenous corticosteroid treatment (Answer A is correct). Because this toxicity is immune related and treatment with steroids is necessary to

suppress the immune system in order to reverse the toxicity, loperamide treatment would be inappropriate (Answer B is incorrect). Although discontinuing immunotherapy can be considered for a grade 3 colitis toxicity, it is not required, and the patient may be able to restart therapy once he improves; however, immediate intervention is needed with corticosteroid treatment (Answer C is incorrect). The proper dose of steroid is 1–2 mg/kg/day either orally or intravenously, depending on the severity of the toxicity (Answer D is incorrect).

Pharmacokinetics: A Refresher

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Pharmacokinetics: A Refresher

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Learning Objectives

1. Solve pharmacotherapy problems using basic pharmacokinetic concepts, including bioavailability, volume of distribution, clearance, and the elimination rate constant.
2. Describe clinically relevant issues related to drug transport proteins, cytochrome P450 metabolism, pharmacogenetics, and drug sampling and interpretation.
3. Describe specific pharmacokinetic characteristics and target concentrations of commonly used therapeutic agents, including aminoglycosides, vancomycin, phenytoin, valproic acid, and digoxin, as well as pharmacokinetic alterations in patients with renal and hepatic disease.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. J.H., a 65-year-old woman (weight 65 kg), was recently initiated on tobramycin and piperacillin/tazobactam for the treatment of hospital-acquired pneumonia. After the first tobramycin dose of 120 mg (infused from noon to 1:00 p.m.), serum tobramycin concentrations are obtained. They are 4.4 mg/L at 3:00 p.m. and 1.2 mg/L at 7:00 p.m. Which is the best assessment regarding the calculation of tobramycin pharmacokinetic parameters in this patient?
   A. Data are sufficient to determine the half-life but not the volume of distribution (Vd).
   B. Data are sufficient to determine both the half-life and the Vd.
   C. Data are insufficient to determine either the half-life or the Vd.
   D. Data are sufficient to determine the Vd but not the half-life.

2. P.L. is a 60-year-old woman (60 kg) recently initiated on gentamicin and clindamycin. After the first gentamicin dose of 110 mg (infused from 6:00 p.m. to 6:30 p.m.), serum gentamicin concentrations are obtained. They are 3.6 mg/L at 7:30 p.m. and 0.9 mg/L at 11:30 p.m. Which is the best assessment of this patient's gentamicin pharmacokinetic parameters?
   A. The half-life is about 2 hours.
   B. The half-life is about 3 hours.
   C. The maximum concentration (Cmax) is about 3.8 mg/L.
   D. The Vd is about 11.6 L.

3. R.O. is a 74-year-old woman initiated on gentamicin 100 mg intravenously every 24 hours for pyelonephritis. When gentamicin was started, her serum creatinine (SCr) was 1.8 mg/dL. She also has a diagnosis of heart failure and is experiencing fluid overload. Today, 5 days after starting gentamicin, her SCr has decreased to 1.1 mg/dL, and the addition of furosemide and enalapril has resulted in a significant amount of fluid removal. Which most likely happened to the gentamicin half-life in R.O. during her hospitalization?
   A. Her clearance increased, which increased her Vd and decreased her half-life.
   B. Her clearance increased, which increased her elimination rate constant and decreased her half-life.
   C. Her Vd decreased, which increased her clearance and decreased her half-life.
   D. Her Vd decreased, which increased her elimination rate constant and increased her half-life.

4. A patient receives vancomycin 1000 mg intravenously every 24 hours for a serious methicillin-resistant *Staphylococcus aureus* infection and has a trough concentration, obtained 30 minutes before the next dose, of 6 mg/L, with an estimated vancomycin 24-hour AUC of 210 mg * hour/L. Which regimen is best for this patient if the goal AUC/MIC is 400–600 (assuming an MIC of 1 mg/L)?
   A. Maintain the dosage at 1000 mg intravenously every 24 hours.
   B. Lower the dosage to 500 mg but keep the interval at every 24 hours.
   C. Keep the dosage at 1000 mg but shorten the interval to every 12 hours.
   D. Lower the dosage to 500 mg and shorten the interval to every 12 hours.

5. R.K., a 39-year-old man who is HIV positive, receives a diagnosis of cryptococcal meningitis and begins taking amphotericin B and flucytosine.

You want to keep flucytosine peak concentrations at 50–100 mg/L. Assuming a steady-state trough concentration of 25 mg/L, dosing every 6 hours, and 100% bioavailability, which is the best dosage to achieve a peak concentration within the desired range (flucytosine volume of distribution of 0.7 L/kg and half-life of 3 hours)?

A. 12.5 mg/kg.

B. 37.5 mg/kg.

C. 75 mg/kg.

D. 150 mg/kg.

6. L.R. is a 49-year-old man with diabetes mellitus and renal failure on hemodialysis. He was recently in a car accident and sustained a head trauma. He currently receives phenytoin 100 mg intravenously three times a day, and his most recent concentration was 5.6 mg/L. You are asked to suggest a new dosage to achieve a concentration within the therapeutic range. Laboratory results include sodium 145 mEq/L, potassium 3.9 mEq/L, chloride 101 mEq/L, carbon dioxide 26 mEq/L, blood urea nitrogen (BUN) 95 mg/dL, SCr 5.4 mg/dL, glucose 230 mg/dL, and albumin (Alb) 2.8 g/dL. Which is the best recommendation?

   A. Increase the dosage to 200 mg intravenously three times a day.

   B. Increase the dosage to 200 mg intravenously two times a day.

   C. Decrease the dosage to 100 mg intravenously two times a day.

   D. Keep the dosage the same.

7. You are asked how the fluorescence polarization immunoassay (TDx) and enzyme multiplied immunoassay technique (EMIT) assays compare with each other. Which statement is most accurate?

   A. Although both are immunoassays, one uses antibodies to bind the molecule of interest, whereas the other uses antigens.

   B. Although both are immunoassays, one uses an enzyme label, whereas the other uses a radioisotope label.

   C. Although both are immunoassays, one uses an enzyme label, whereas the other uses a fluorescent label.

   D. They are both names for the same assay technique.

8. An older adult is seen in the morning medicine clinic for a routine follow-up. Medication history includes digoxin 0.25 mg/day by mouth, furosemide 40 mg/day by mouth, and potassium chloride 10 mEq/day by mouth. All doses were last taken at 8:00 a.m. today at home. The patient has vague complaints of stomach upset, which began 2 days ago, but is otherwise in no apparent distress. A serum digoxin concentration obtained today at 10:00 a.m. is 2.5 mcg/L. Which statement best describes what should be done next?

   A. Admit the patient for administration of digoxin Fab.

   B. Tell the patient to skip tomorrow's dose of digoxin and begin 0.125 mg/day by mouth.

   C. Administer a dose of activated charcoal.

   D. Maintain the same digoxin dose and check another serum digoxin concentration at an appropriate time.

9. A research group is analyzing the relationship between various independent patient demographics (e.g., age, height, weight, albumin, creatinine clearance [CrCl]) and phenytoin pharmacokinetics. Which is the best statistical test to use in assessing the relationship?

   A. One-way analysis of variance.

   B. Analysis of covariance.

   C. Multiple regression.

   D. Spearman rank correlation.

10. N.T. is a 24-year-old woman receiving valproic acid for tonic-clonic seizures. Her most recent trough valproic acid concentration was 22 mg/L. Her most recent albumin concentration was 4.1 g/dL. Given this albumin, which recommendation is best regarding her dosage?

    A. Continue with the current dosage; the concentration is close enough to the therapeutic range.

    B. Assess adherence and increase her dosage; the concentration is below the therapeutic range.

    C. Decrease her dosage; the concentration is slightly above the therapeutic range.

D. Assess adherence and then check a free valproic acid concentration and adjust accordingly.

11. N.G. is a 54-year-old woman with a recent head injury. She comes to your pharmacy with complaints about the prescription for acetaminophen with codeine you dispensed to her yesterday. She says that it does not seem any stronger than when she uses acetaminophen alone. On her profile, you notice results from pharmacogenetic testing performed 3 years ago that show she is a CYP2D6 poor metabolizer. In addition to acetaminophen and codeine, she is receiving aspirin, clopidogrel, omeprazole, lisinopril, citalopram, metoprolol succinate, docusate, and trazodone. Which is the best explanation why N.G. does not seem to benefit from codeine?
    A. Omeprazole inhibited CYP2C19, causing less codeine activation.
    B. Codeine is not as active in N.G. because she is a CYP2D6 poor metabolizer.
    C. Codeine is metabolized faster in N.G., leading to lower concentrations.
    D. Metoprolol inhibited CYP2C9, causing less codeine activation.

12. At your hospital you are responsible for making dosing adjustments in patients with poor renal function. While working with you, a student asks why you are using the Cockcroft-Gault method for estimating CrCl instead of the newer Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations. Which is the best response to provide to this student?
    A. MDRD and CKD-Epi are not as good estimates of renal function and may lead to inappropriate changes in drug dosing.
    B. MDRD and CKD-Epi were developed in an ambulatory care population and cannot be used for hospitalized patients.
    C. The Cockcroft-Gault estimate of CrCl has units that are different from the glomerular filtration rate estimates calculated using the MDRD and CKD-Epi equations.
    D. Recommendations for renal dosing adjustments in package inserts are usually based on CrCl estimates using the Cockcroft-Gault equation.

13. An assay used for therapeutic drug monitoring at your institution has a low sensitivity and low precision. Which is the best statement about the impact of this assay on drug monitoring?
    A. The assay may be unable to detect low concentrations, and it will report highly variable values when repeatedly run on the same sample.
    B. The assay may be unable to detect low concentrations, and it will consistently over- or under-predict the true concentration.
    C. The assay will be unable to differentiate between like substances, and it will consistently over- or under-measure the true concentration.
    D. The assay will be unable to differentiate between like substances, and it will report highly variable values when repeatedly run on the same sample.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.1 - 1.1.3, 1.1.6, 1.1.8, 1.1.10 - 1.1.12

Patient Cases

1. H.R. is receiving vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia. H.R. has chronic kidney disease. A 1-g intravenous dose of vancomycin is given at noon on March 21. A concentration obtained at 2:00 p.m. on March 21 is 27.8 mg/L. After no additional doses, a concentration obtained at 2:00 p.m. on March 24 is 14.1 mg/L. If you were to give a 1-g dose at 4:00 p.m. on March 24 and your goal trough concentration to achieve an appropriate AUC/MIC ratio was 10–15 mg/L, which would be the best time to give the next dose?
   A. 1 day after the dose on the 24th.
   B. 3 days from the dose on the 24th.
   C. 6 days from the dose on the 24th.
   D. Insufficient information to calculate when to redose.

2. After the administration of 100 mg of a drug intravenously and 200 mg of the same drug by mouth, the areas under the curves (AUCs) are 50 and 25 mg*hr/L, respectively. Which best describes the bioavailability of this drug?
   A. 25%.
   B. 37.5%.
   C. 50%.
   D. 100%.

I. BASIC PHARMACOKINETIC RELATIONSHIPS

Table 1 contains definitions of terms.

Table 1. Pharmacokinetic Term Definitions

AUC	Area under the curve
AUC_{ev}	Area under the curve after an extravascular dose
AUC_{iv}	Area under the curve after an intravenous dose
Cmax	Maximum concentration
Cmin	Minimum concentration
C_0	Concentration at time zero
C_{ss}	Concentration at steady state
$C_{ss\ avg}$	Average concentration at steady state
$C_{ss\ max}$	Maximum concentration at steady state
$Dose_{EV}$	Dose given extravascularly
$Dose_{IV}$	Dose given intravenously
F	Bioavailability
k	Elimination rate constant
R_0	Rate of infusion
τ	Dosing interval
t	Time of the intermittent infusion
t_i	Time from initiation of the continuous infusion
Vd	Volume of distribution

A. Absorption $F = \frac{dose_{iv} * AUC_{ev}}{dose_{ev} * AUC_{iv}}$

B. Distribution

Rapid intravenous (or oral) bolus: $Vd = \frac{F * dose}{C_0}$

Continuous intravenous infusion at steady state: $Vd = \frac{R_0}{k * C_{ss}}$

Continuous intravenous infusion before steady state: $Vd = \frac{R_0}{C * k}(1-e^{-kt_i})$ and $C = \frac{R_0}{V_d * k}(1-e^{-kt_i})$

Multiple intravenous bolus at steady state: $Vd = \frac{dose}{C_{ss\,max} * (1-e^{-k\tau})}$

Multiple intermittent intravenous infusion at steady state: $Vd = \frac{R_0}{k} * \frac{1-e^{-kt}}{C_{max} - (C_{min} * e^{-kt})}$

$C_{ss\,max} = \frac{R_0 * (1-e^{-kt})}{V_d * k * (1-e^{-kt})}$ $C_{ss\,min} = C_{ss\,max} * e^{-k(\tau - t)}$

C. Clearance

$Clearance = \frac{dose}{AUC}$ $k = \frac{Cl}{V_d}$ $k = \frac{(1nC_1 - 1nC_2)}{(t_2 - t_1)}$ $t_{1/2} = \frac{0.693}{k}$

Continuous intravenous infusion at steady state: $Clearance = \frac{R_0}{C_{ss}}$

Continuous intravenous infusion before steady state: $Clearance = \frac{R_0}{C} * (1 - e^{-kt_i})$

Multiple intravenous (or oral) bolus at steady state: $Clearance = \frac{\frac{F*dose}{\tau}}{C_{ss,avg}}$

$\tau = \frac{(1nC_{max} - 1nC_{min})}{k}$

II. ABSORPTION

A. First-Pass Effect

1. Blood that perfuses almost all the gastrointestinal (GI) tissues passes through the liver by means of the hepatic portal vein.
   a. Fifty percent of the rectal blood supply bypasses the liver (middle and inferior hemorrhoidal veins).
   b. Drugs absorbed in the buccal cavity bypass the liver.

2. Examples of drugs with significant first-pass effect

Amitriptyline	Diltiazem	Labetalol	Propafenone
Atorvastatin	Doxepin	Metoprolol	Propranolol
Buprenorphine	Felodipine	Morphine	Raloxifene
Buspirone	Imipramine	Nifedipine	Simvastatin
Diazepam	Isosorbide dinitrate	Nitroglycerin	Verapamil

B. Enterohepatic Recirculation (Table 2)
   1. Drugs are excreted through the bile into the duodenum, metabolized by the normal flora in the GI tract, and reabsorbed into the portal circulation.
   2. Occurs with drugs that have biliary (hepatic) elimination and good oral absorption
   3. Drug is concentrated in the gallbladder and expelled on sight, smell, or ingestion of food.

Table 2. Examples of Compounds Excreted in Bile and Subject to Enterohepatic Cycling

Compound	Entity in Bile
Chloramphenicol	Glucuronide conjugate
Digoxin	Parent
Estrogens	Parent
Imipramine	Parent and desmethyl metabolite
Indomethacin	Parent and glucuronide
Nafcillin	Parent
Rifampin	Parent
Sulindac	Glucuronides of parent and metabolites
Testosterone	Conjugates
Tiagabine	Glucuronide conjugate
Valproic acid	Glucuronide conjugates
Vitamin A	Conjugates

Patient Case

3. Which statement best describes P-glycoprotein?
   A. It is a plasma protein that binds basic drugs.
   B. It transfers drugs through the GI mucosa, increasing absorption.
   C. It diminishes the effect of cytochrome P450 3A4 (CYP3A4) in the GI mucosa.
   D. It is an efflux pump that decreases GI mucosal absorption.

C. P-Glycoprotein (*ABCB1*)
   1. P-glycoprotein is an efflux pump (located in the esophagus, stomach, and small and large intestines) that pumps drugs back into the GI lumen; it is a more important factor in drug interactions during drug absorption than intestinal CYP3A4.
   2. Both CYP3A4 and P-glycoprotein are located in small intestinal enterocytes and work together to decrease the absorption of xenobiotics.
   3. Most CYP3A4 substrates are also P-glycoprotein substrates.
   4. Many CYP3A4 inhibitors/inducers also inhibit/induce P-glycoprotein, leading to an increase or decrease in bioavailability.

Table 3. P-glycoprotein Drug Interactions

Substrate	Enhanced P-gp effects (decreased substrate serum concentrations)	Diminished P-gp effects (increased substrate serum concentrations)
Apixaban Colchicine Cyclosporine Dabigatran Digoxin Edoxaban Ranolazine Rivaroxaban Tacrolimus	Carbamazepine Phenytoin Rifampin St. John's wort	Amiodarone Clarithromycin Dronedarone Erythromycin Hepatitis C direct-acting antivirals Itraconazole Ivacaftor Ketoconazole Propafenone Quinidine Ranolazine Verapamil

III. DISTRIBUTION

A. Apparent Vd: Proportionality constant that relates the amount of drug in the body to an observed concentration of drug

B. Protein Binding (Table 4)

Table 4. Common Proteins Involved in Drug Protein Binding

Protein	Types of Drugs Bound	Molecular Weight	Normal Concentrations	
			g/L	mcmol/L
Albumin	Acidic	65,000	35–50	500–700
α-1-Acid glycoprotein	Basic	44,000	0.4–1.0	9–23
Lipoprotein	Lipophilic and basic	200,000–3,400,000	Variable	Variable

C. P-Glycoprotein
   1. Functions as an efflux pump on the luminal surface of the blood-brain barrier, limiting entry to the central nervous system
   2. It may be especially important with opioids: Induction of P-glycoprotein by chronic use of opioids may decrease the opioid effect (tolerance).
   3. P-glycoprotein is also found in tumor cells, resulting in the efflux of chemotherapeutic agents from the cell and, ultimately, multidrug resistance.

IV. CLEARANCE

A. Metabolic enzymes (Table 5) and transport proteins (Table 6) involved in drug clearance

Table 5. Enzymes Involved in Drug Metabolism

Oxygenases CYPs Monoamine oxygenases Alcohol dehydrogenases Aldehyde dehydrogenases Xanthine dehydrogenases	**Hydrolytic enzymes** Esterases Amidases Epoxide hydrolases Dipeptidases
Conjugating enzymes Uridine diphosphate–glucuronyl transferases Glutathione *S*-transferase Acetyltransferases Methyltransferases	

CYP = cytochrome P450.

Table 6. Drug Transport Proteins

Transport Protein Superfamily	Transport Protein (Gene [Protein])	Location and Function	Drugs Affected by Transport Protein	Inhibitors of Transport Protein
SLC	*SLC01A2* [OATP1A2]	Hepatocyte: Bile acid uptake	Digoxin Levofloxacin Methotrexate Statins	Naringin
	SLCO1B1 [OATP1B1]	Hepatocyte: Hepatic uptake of drugs	Hepatitis C direct-acting antivirals Rifampin Statins Valsartan	Clarithromycin Cyclosporine Gemfibrozil Hepatitis C direct-acting antivirals Teriflunomide
	SLCO1B3 [OATP1B3]	Hepatocyte: Hepatic uptake of drugs	Digoxin Fexofenadine Rifampin Statins	Cyclosporine Erythromycin Teriflunomide
	SLC22A1, SLC22A2, SLC22A6, SLC22A8 [OAT and OCT]	Hepatocyte: Hepatic uptake of drugs Renal tubule (interstitial side): Secretion of drugs	Dofetilide[b] Methotrexate[a] Organic anions and cations[b] Salicylate[a] Tetracycline[a] Zidovudine[a]	Cimetidine Teriflunomide
	SLCO2B1 [OATP2B1]	Hepatocyte: Hepatic uptake of drugs	Fexofenadine Glyburide Statins	Cyclosporine Gemfibrozil
	SLC15A1, SLC15A2 [PEPT1, PEPT2]	Renal tubule Intestinal enterocytes	Captopril Cephalexin Enalapril Valacyclovir	
	SLC47A1, SLC47A2 [MATE1, MATE2-K]	Renal tubule	Metformin	Cimetidine

Table 6. Drug Transport Proteins *(Cont'd)*

Transport Protein Superfamily	Transport Protein (Gene [Protein])	Location and Function	Drugs Affected by Transport Protein	Inhibitors of Transport Protein
ABC	*ABCB11* [BSEP]	Hepatocyte: Bile acid excretion into bile	Pravastatin	
	ABCC2, 3, 4, and *5* [MRP2, 3, 4, and 5]	Hepatocyte: Excreting water-soluble drugs and metabolites into blood Renal tubule (luminal side): Secretion of drugs	Glucuronide, sulfate, and glutathione metabolites[a] Methotrexate[a] Pravastatin[a] Rifampin[a]	Probenecid Ritonavir
	ABCB1 [MDR1] (P-glycoprotein)	Hepatocyte: See text in handout Renal tubule (luminal side): See text in handout	See text	Amiodarone Quinidine Verapamil
	ABCB4 [MDR3]	Hepatocyte	Digoxin Paclitaxel Vinblastine	Itraconazole Ritonavir
	ABCG2 [BCRP]	Hepatocyte: Biliary excretion	Cladribine Daunorubicin Doxorubicin Imatinib Methotrexate Mitoxantrone Ozanimod Rosuvastatin Topotecan	Omeprazole Ritonavir Teriflunomide

[a]Drugs affected by transport proteins in hepatocytes.

[b]Drugs affected by transport proteins in the renal tubule.

Patient Case

4. A renal transplant patient receiving cyclosporine is given a diagnosis of community-acquired pneumonia. The patient is admitted to the hospital and initiated on ceftriaxone and a macrolide. A physician asks you to choose a macrolide that will not interact with the patient's cyclosporine. Which is the best choice to avoid this potential drug interaction?

   A. Erythromycin.

   B. Clarithromycin.

   C. Azithromycin.

   D. Doxycycline (because all macrolides will interact).

B. Cytochrome P450

   1. Introduction

      a. A group of heme-containing enzymes responsible for phase 1 metabolic reactions

      b. Characteristic absorbance of light at 450 nm (hence CYP450)

      c. Located primarily in the membranes of the smooth endoplasmic reticulum in the liver, small intestine, brain, lung, and kidney

      d. Encoded by a supergene family and subfamily; separate genes code for different isoenzymes

      e. Drugs generally have a high affinity for one particular CYP, but most drugs also have secondary pathways (see Table 7).

Table 7. CYP Drug Interactions

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4	
Induction	Carbamazepine Modafinil Nafcillin Omeprazole Rifampin	Enzalutamide Phenobarbital Phenytoin Rifampin Rifapentine	Carbamazepine Efavirenz Enzalutamide Phenobarbital Prednisone Rifampin St. John's wort	Not an inducible enzyme	Carbamazepine Efavirenz Enzalutamide Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin	Pioglitazone Rifabutin Rifampin Rifapentine St. John's wort
Inhibition	Amiodarone Cimetidine Ciprofloxacin Diltiazem Efavirenz Erythromycin Fluvoxamine Mexiletine Norfloxacin	Amiodarone Efavirenz Fenofibrate Fluconazole Fluvoxamine Isoniazid Lovastatin Metronidazole Paroxetine Sertraline Sulfamethoxazole Trimethoprim Voriconazole	Cimetidine Esomeprazole Fluoxetine Fluvoxamine Isoniazid Ketoconazole Lansoprazole Modafinil Omeprazole Oxcarbazepine Pantoprazole Topiramate Voriconazole	Amiodarone Bupropion Celecoxib Chlorpheniramine Cimetidine Cinacalcet Citalopram Diphenhydramine Duloxetine Escitalopram Fluoxetine Haloperidol Methadone Metoclopramide Midodrine Paroxetine Propafenone Quinidine Ritonavir Sertraline Terbinafine Thioridazine	Amiodarone Aprepitant Atazanavir Boceprevir Cimetidine Clarithromycin Darunavir Delavirdine Diltiazem Erythromycin Fluconazole (large doses)	Fluvoxamine Fosamprenavir Imatinib Itraconazole Ketoconazole Nelfinavir Ritonavir Telaprevir Verapamil Voriconazole

Table 7. CYP Drug Interactions *(Cont'd)*

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4	
Substrates	Acetaminophen Amitriptyline Caffeine Clomipramine Clozapine Cyclobenzaprine Estradiol Fluvoxamine Haloperidol Imipramine Mirtazapine Olanzapine Riluzole Ropinirole *R*-warfarin Theophylline Zolmitriptan	Amitriptyline Celecoxib Diclofenac Fluoxetine Glimepiride Glipizide Glyburide Ibuprofen Indomethacin Irbesartan Losartan Phenytoin Rosuvastatin *S*-warfarin Siponimod Tamoxifen	Amitriptyline Cilostazol Citalopram Clomipramine Clopidogrel Diazepam Imipramine Lansoprazole Naproxen Omeprazole Pantoprazole Phenobarbital Phenytoin Propranolol	Amitriptyline Aripiprazole Atomoxetine Carvedilol Clomipramine Clozapine Codeine Dextromethorphan Donepezil Duloxetine Flecainide Fluoxetine Fluvoxamine Haloperidol Hydrocodone Imipramine Metoprolol Mirtazapine Nebivolol Nortriptyline Oxycodone Paroxetine Propafenone Propranolol Risperidone Tamoxifen Thioridazine Timolol Tramadol Trazodone Venlafaxine	Alprazolam Amiodarone Amlodipine Aprepitant Aripiprazole Atorvastatin Boceprevir Buprenorphine Buspirone Carbamazepine Cilostazol Citalopram Clarithromycin Cyclosporine Dapsone Darunavir Delavirdine Diazepam Diltiazem Donepezil Efavirenz Eplerenone Erlotinib Erythromycin Ethinyl estradiol Felodipine Fentanyl Finasteride Fosamprenavir Gefitinib Imatinib Irinotecan Itraconazole Ketoconazole Lapatinib Lidocaine	Lovastatin Methadone Midazolam Mirtazapine Nateglinide Nevirapine Nifedipine Quetiapine Quinidine Repaglinide Rifabutin Ritonavir Sertraline Sibutramine Sildenafil Simvastatin Siponimod Sirolimus Sorafenib Sunitinib Tacrolimus Telaprevir TCAs (amitriptyline, clomipramine, imipramine) Tiagabine Trazodone Triazolam Vardenafil Verapamil Voriconazole Zaleplon Ziprasidone Zolpidem Zonisamide

f. Nomenclature

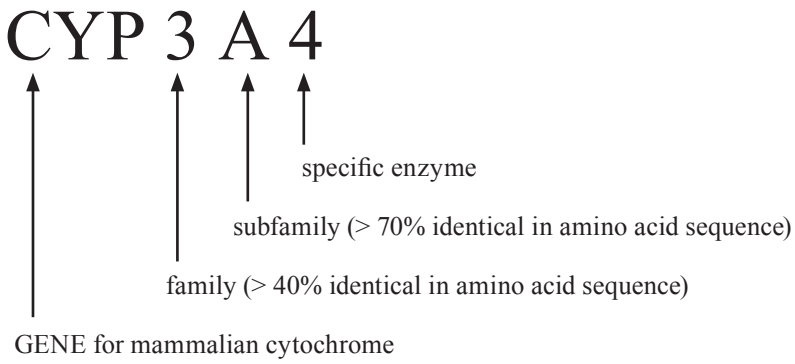
CYP 3 A 4
specific enzyme
subfamily (> 70% identical in amino acid sequence)
family (> 40% identical in amino acid sequence)
GENE for mammalian cytochrome

Figure 1. Nomenclature.

2. Distribution of CYP isoenzymes in human liver

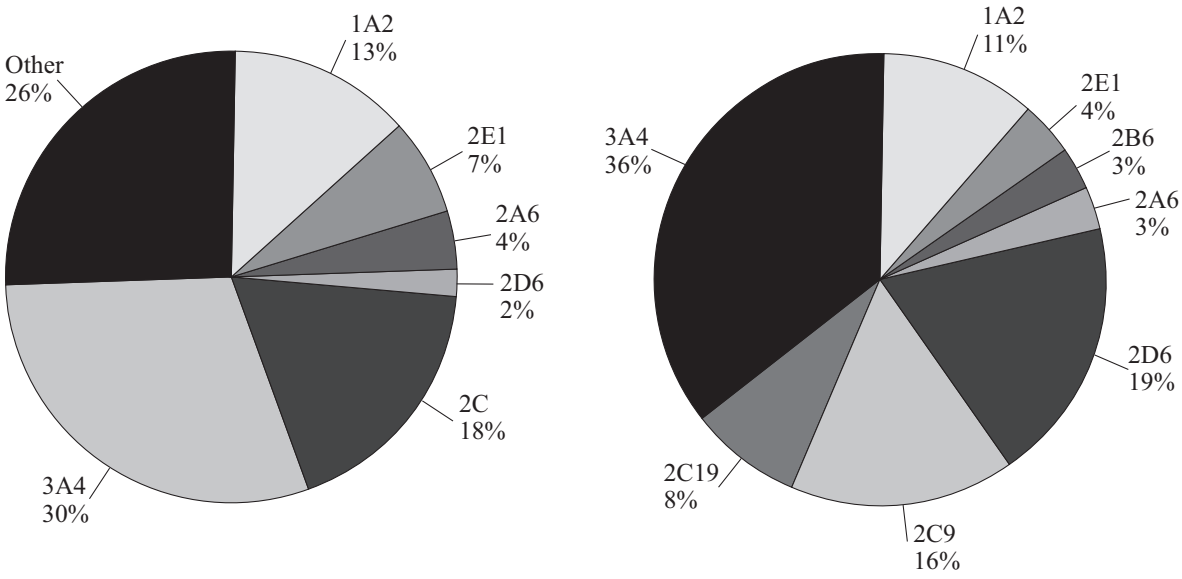

Figure 2. Distribution of CYP isoenzymes in human liver.

3. Distribution of CYP isoenzymes in human GI tract

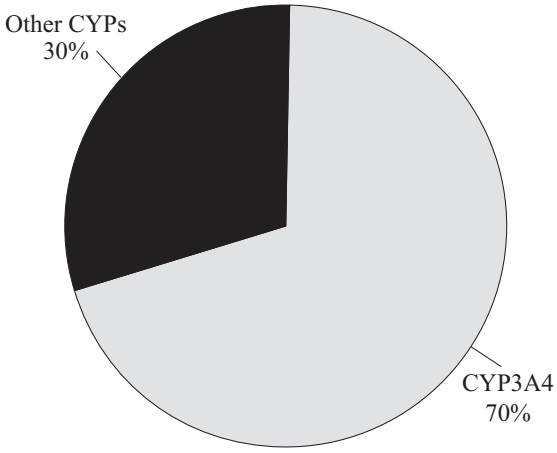

Figure 3. Distribution of CYP isoenzymes in human gastrointestinal tract.

4. Characteristics of CYP metabolism
   a. Inhibition is substrate-independent.
   b. Some substrates are metabolized by more than one CYP (e.g., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]).
   c. Enantiomers may be metabolized by different CYP isoenzymes (e.g., R- vs. S-warfarin).
   d. Differences in inhibition may exist in the same class of agents (e.g., fluoroquinolones, azole antifungals, macrolides, calcium channel blockers, histamine-2 blockers).
   e. Substrates can also be inhibitors (e.g., erythromycin, verapamil, diltiazem).

f. Most inducers and some inhibitors can affect more than one isozyme (e.g., cimetidine, ritonavir, fluoxetine, erythromycin).
g. Inhibitors may affect different isozymes at different dosages (e.g., fluconazole inhibits CYP2C9 at dosages of 100 mg/day or greater and inhibits CYP3A4 at dosages of 400 mg/day or greater).

5. Drug interactions
   a. Induction – Adaptive increase in enzyme activity in response to another agent – Slow, regulatory process
      i. Induction is dose-dependent.
      ii. Onset – Usually begins after several days, with a maximal effect within 2 weeks (somewhat dependent on the potency and half-life of the inducer)
      iii. Offset – Usually longer to eliminate enzymes than to generate enzymes; enzyme activity returns to normal within 2–3 weeks (somewhat dependent on the half-life of the inducer)
   b. Inhibition – Direct action on an enzyme that renders the enzyme inactive
      i. Inhibition is dose-dependent.
      ii. Onset – Quicker than induction (inhibition begins as soon as the inhibiting agent is in the system), but dependent on the half-life of the inhibiting agent and the substrate (i.e., time to steady state for both agents)
      iii. Offset – Effect is gone as soon as the inhibiting agent is eliminated.

C. P-Glycoprotein
1. P-glycoprotein is an efflux pump that pumps drugs into the bile; the clinical effect of P-glycoprotein drug interactions in the bile is unknown.
2. P-glycoprotein pumps drugs from renal tubules into the urine; it also potentially limits the degree of reabsorption.
3. Examples of drug interactions: quinidine/digoxin, cyclosporine/digoxin, and propafenone/digoxin

Patient Case

5. W.T., a 62-year-old man who presents to the emergency department with chest pain, is given a diagnosis of a non-ST-segment elevation myocardial infarction. He goes to the catheterization laboratory, where two drug-eluting stents are placed. After stent placement, he is initiated on aspirin 81 mg daily and clopidogrel 75 mg daily. A CYP2C19 pharmacogenetic test shows that he is a poor metabolizer (*CYP2C19*3/*3* genotype). The patient also receives losartan 25 mg daily, carvedilol 25 mg twice daily, amitriptyline 100 mg daily, acetaminophen 500 mg as needed, and atorvastatin 40 mg daily. Given his pharmacogenetic profile, which is most likely to occur in this patient?

   A. He will form a metabolite of clopidogrel that will block the action of aspirin, increasing the risk of a thrombotic event.
   B. He will not activate clopidogrel well, increasing the risk of a thrombotic event.
   C. He will not metabolize clopidogrel well, increasing the risk of a bleeding event.
   D. He will overproduce an active metabolite of clopidogrel, increasing the risk of a bleeding event.

D. Pharmacogenetics
1. Population in general is divided into poor, intermediate, extensive, and ultrarapid metabolizers; therefore, metabolism is considered polymorphic.
2. Definition of polymorphism: Coexistence of more than one genetic variant (alleles), which are stable components in the population (more than 1% of population)
3. Clear antimode (separation between the two populations) results

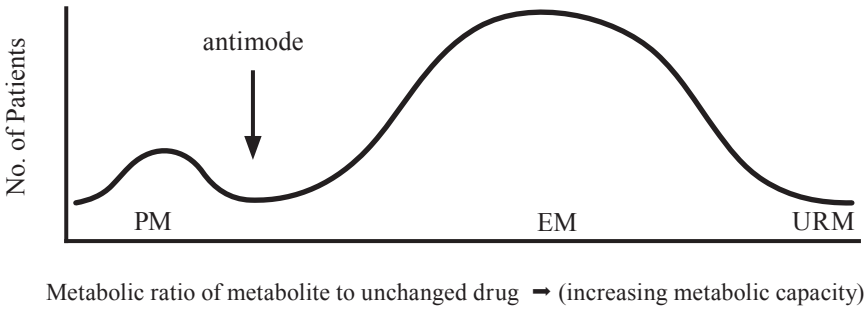

Figure 4. Distribution of patients in a drug that follows polymorphic metabolism.
EM = extensive metabolizer; PM = poor metabolizer; URM = ultrarapid metabolizer.

4. Phenotype: Expression of the trait; interaction of gene with environment
   a. Manifestation of the trait clinically
   b. Not necessarily constant
5. Genotype: Genetic makeup
6. Pharmacogenetics in clinical practice (Table 8)

Table 8. Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug metabolism	*CYP2C9*	*CYP2C9*2 (70%–90% activity)* *CYP2C9*3 (10%–30% activity)*	NSAIDs Phenytoin Siponimod Warfarin
Drug metabolism	*CYP2C19*	*CYP2C19*2 (poor)* *CYP2C19*3 (poor)* *CYP2C19*17 (ultrarapid)* *CYP2C19*4 (null variant)*	Clopidogrel Diazepam Omeprazole SSRIs Tricyclic antidepressants Voriconazole
Drug metabolism	*CYP2D6*	*CYP2D6*10 (poor)* *CYP2D6*17 (poor)* *CYP2D6*3, *4, and *5 (null)*	Antiarrhythmics Antipsychotics Beta blockers Codeine, hydrocodone, oxycodone Dextromethorphan SSRIs Tamoxifen Tramadol Tricyclic antidepressants
Drug metabolism	*UDP-glucuronosyltransferases*	*UGT1A1*6* *UGT1A1*28* *UGT2B7*2* *UGT2B7*28*	Atazanavir Irinotecan Mycophenolate NSAIDs
Drug metabolism	*N*-acetyltransferase	*NAT2*4* *NAT2*5* *NAT2*6* *NAT2*7*	Hydralazine Isoniazid Sulfasalazine

Table 8. Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions *(Cont'd)*

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug transport	*SLCO1B1*	*SLCO1B1*1A,*1B* *SLCO1B1*5, *15, *17*	Simvastatin
Drug target	*VKOR*	*VKORC1*2 (increases)* *VKORC1*3 (decreases)*	Warfarin
Adverse drug reactions	*HLA-B*	*HLA-B*5701*	Abacavir
		*HLA-B*5801*	Allopurinol
		*HLA-B*1502*	Carbamazepine, phenytoin

NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

6. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   a. Designed to facilitate translation of pharmacogenetics information from research to clinical practice
   b. Developing guidelines for use of pharmacogenetic test results in drug dosing
   c. Focused on specific drug-gene pairs (Table 9)

Table 9. CPIC Clinical Recommendations for Drug-Gene Pairs

Drug	Gene	Recommendation
Abacavir	*HLA-B*	Avoid using because of increased incidence of hypersensitivity reactions in patients with the *HLA-B*57:01* allele
Allopurinol	*HLA-B*	Avoid using because of increased incidence of severe cutaneous adverse reactions in patients with the *HLA-B*58:01* allele
Aminoglycosides: Amikacin, Gentamicin, Tobramycin	*MT-RNR1*	Avoid using in patients with certain variants of MT-RNR1 because of increased risk of aminoglycoside-induced hearing loss.
Atazanavir	*UGT1A1*	For patients who carry 2 decreased function *UGT1A1* alleles, increased risk of jaundice and subsequent nonadherence Consider alternative agents
Atomoxetine	*CYP2D6*	Slower dose titration in intermediate and poor metabolizers. In addition, obtain plasma concentrations 2–4 hr after dosing instead of 1–2 hr
Capecitabine/5-fluorouracil/ tegafur	*DPYD*	Avoid using in poor metabolizers. Decrease dose by 50% in intermediate metabolizers.
Carbamazepine/oxcarbazepine	*HLA-A* *HLA-B*	Avoid using because of increased incidence of severe cutaneous adverse reactions in patients with the *HLA-A*31:01* or *HLA-B*15:02* allele
Clopidogrel	*CYP2C19*	Normal dosing for ultrarapid, rapid, and normal metabolizers; alternative antiplatelet therapy in intermediate or poor metabolizers
Codeine Tramadol	*CYP2D6*	Avoid using codeine or tramadol because of potential toxicity or lack of efficacy in ultrarapid and poor metabolizers
Efavirenz	*CYP2B6*	In intermediate and poor metabolizers, consider initiating lower doses of efavirenz (200–400 mg/day)
Irinotecan	*UGT1A1*	Reduce the starting dose of irinotecan for *UGT1A1*28* homozygous patients receiving more than 250 mg/m^2
Ivacaftor	*CFTR*	Recommended only for patients with cystic fibrosis who have certain variants as noted in the package insert

Table 9. CPIC Clinical Recommendations for Drug-Gene Pairs *(Cont'd)*

Drug	Gene	Recommendation
NSAIDs: Celecoxib, Ibuprofen, Meloxicam	*CYP2C9*	In intermediate metabolizers, start with lowest recommended starting dose (celecoxib/ibuprofen) or 50% of lowest recommended starting dose (meloxicam) and titrate to clinical effect. In poor metabolizers, start with 25%–50% of the lowest recommended starting dose and titrate to clinical effect or 25%–50% of the maximum recommended dose (celecoxib/ibuprofen). Do not use meloxicam in poor metabolizers
Ondansetron	*CYP2D6*	Select an alternative drug that is not predominantly metabolized by CYP2D6 (i.e., granisetron) in CYP2D6 ultra-rapid metabolizers
Phenytoin/Fosphenytoin	*CYP2C9* *HLA-B*	Reduce initial dosage by 25% in CYP2C9 intermediate metabolizers with activity score of 1.0 and by 50% in poor metabolizers Severe cutaneous adverse reactions associated with carriers of the *HLA-B*15:02* allele; use an alternative anticonvulsant
PPIs: Lansoprazole Omeprazole Pantoprazole	*CYP2C19*	Increase starting dose by 100% in ultrarapid metabolizers, consider increasing dose by 50%–100% in rapid and normal metabolizers, use standard dose but consider decreasing dose by 50% if used longer than 12 weeks in intermediate and poor metabolizers.
Rasburicase	*G6PD*	Contraindicated in those with G6PD deficiency
Siponimod	*CYP2C9*	Maximum 1 mg dose in poor/intermediate metabolizers (**1/*3, *2/*3*) and 2 mg in normal/intermediate metabolizers (**1/*1, *1/*2, *2/*2*)
SSRIs: Citalopram: 2C19 Escitalopram: 2C19 Sertraline: 2C19 Fluvoxamine: 2D6 Paroxetine: 2D6	*CYP2D6, CYP2C19*	Alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers, and for CYP2C19 poor metabolizers, consider a 50% reduction of recommended starting dosage For CYP2D6 poor metabolizers, consider a 25%–50% reduction of recommended starting dosage
Statins: Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin	*SLCO1B1* *ABCG2* *CYP2C9*	Limit doses of all statins or avoid certain statins in patients with decreased or poor function of *SLCO1B1*. Limit dose of rosuvastatin to no more than 20 mg daily in patients with poor function of *ABCG2*. Limit dose of fluvastatin in patients who are *CYP2C9* intermediate or poor metabolizers.
Tacrolimus	*CYP3A5*	Increase starting dosage by 1.5 to 2 times in CYP3A5 intermediate or extensive metabolizers (not to exceed 0.3 mg/kg/day)
Tamoxifen	*CYP2D6*	Use alternative hormonal therapy for CYP2D6 poor metabolizers (also consider alternative for CYP2D6 intermediate metabolizers)
Thiopurines (azathioprine, 6-mercaptopurine, thioguanine)	*TMPT* *NUDT15*	Dosing recommendations for each drug based on *TMPT* and *NUDT15* genotypes (normal/high, intermediate, and low activity)
Tricyclic antidepressants	*CYP2D6, CYP2C19*	Dosing recommendations for depression based on metabolizer status (ultrarapid, extensive, intermediate, poor) Limited recommendations when using for peripheral neuropathy
Voriconazole	*CYP2C19*	Select an alternative agent that is not dependent on CYP2C19 metabolism, such as isavuconazole, liposomal amphotericin B, or posaconazole, in ultra-rapid and rapid CYP2C19 metabolizers Select an alternative agent that is not dependent on CYP2C19 metabolism in poor CYP2C19 metabolizers, or initiate at a lower-than-normal dose and perform careful therapeutic drug monitoring
Warfarin	*VKORC1/ CYP2C9*	Use available table or algorithms to initiate warfarin dosing based on *VKORC1* and *CYP2C9* genotypes

V. NONLINEAR PHARMACOKINETICS

Patient Case

6. C.M. is a 55-year-old man who is initiated on phenytoin after a craniotomy. His current steady-state phenytoin concentration is 6 mg/L at a dosage of 200 mg/day by mouth. If his affinity constant (Km) is calculated to be 5 mg/L, which is most likely to occur if the dosage is doubled (to 400 mg/day by mouth)?
   A. His concentration will double because phenytoin clearance is linear above the Km.
   B. His concentration will more than double because phenytoin clearance is nonlinear above the Km.
   C. His concentration will stay the same because phenytoin is an autoinducer, and clearance increases with time.
   D. His concentration will increase by only 50% because phenytoin absorption decreases significantly with dosages greater than 300 mg.

A. Michaelis-Menten Pharmacokinetics

$$\text{velocity} = \frac{V_{max} * S}{K_m + S}$$

V_{max} = capacity constant (amount/time)
K_m = affinity constant (amount/volume)
S = substrate concentration (amount/volume)

B. Nonlinear Elimination
   1. Saturation or partial saturation of the elimination pathway

$$\text{rate of elimination (dose)} = \frac{V_{max} * C}{K_m + C}$$

V_{max} = maximum rate of elimination (amount/time)
K_m = concentration where elimination is ½ V_{max} (affinity constant)
C = drug concentration

   2. Note: Nonlinearity occurs when concentration is at or above K_m.
      Example: Phenytoin
      a. V_{max} normal = 7 mg/kg/day
      b. K_m normal = 5.6 mg/L
      c. 50% variability between individuals

VI. NONCOMPARTMENTAL PHARMACOKINETICS

A. Why Noncompartmental Pharmacokinetics?
   1. Identification of the "correct" model is often impossible.
   2. A compartmental view of the body is unrealistic.
   3. Linear regression is unnecessary; it is easier to automate analysis.
   4. Requires fewer and less stringent assumptions
   5. More general methods and equations
   6. There is no need to match all data sets to the same compartmental model.

B. Definitions

1. Zero moment concentration versus time curve
   - Area under the curve (AUC)

$$AUC = \sum \frac{(C_{n+1} + C_n)}{2} * (t_{n+1} - t_n)... + \frac{C_{last}}{k}$$

2. First moment concentration * time versus time curve
   - Area under the first moment curve (AUMC)

$$AUMC = \sum \frac{(C_{n+1} * t_{n+1} + C_n * t_n)}{2} * (t_{n+1} - t_n)... + \frac{C_{last} * t_{last}}{k} + \frac{C_{last}}{k^2}$$

3. Mean residence time (MRT)

$$MRT = \frac{AUMC}{AUC}$$

4. Mean absorption time (MAT)

$$MAT = MRT_{ev} - MRT_{iv}$$

C. Pharmacokinetic Parameter Estimation

1. Clearance

$$Clearance = \frac{dose}{AUC}$$

2. Vd at steady state

$$V_{ss} = \frac{dose * AUMC}{AUC^2}$$

3. Elimination rate constant

$$k = \frac{1}{MRT}$$

4. Absorption rate constant

$$k_a = \frac{1}{MAT}$$

5. Bioavailability

$$F = \frac{D_{iv} * AUC_{ev}}{D_{ev} * AUC_{iv}}$$

VII. DATA COLLECTION AND ANALYSIS

A. Timing of Collection

1. Ensure completion of absorption and distribution phases (especially digoxin [8–12 hours] and aminoglycosides [30 minutes after infusion]).
2. Ensure completion of redistribution after dialysis (especially aminoglycosides [3–4 hours after hemodialysis]).

B. Specimen Requirements

1. Whole blood: Use anticoagulated tube. Examples: cyclosporine, amiodarone
2. Plasma: Use anticoagulated tube and centrifuge; clotting proteins and some blood cells are maintained.
3. Serum: Use red top tube, allow to clot, and centrifuge. Examples: most analyzed drugs including aminoglycosides, vancomycin, phenytoin, and digoxin

Patient Case

7. A drug assay is touted as having high specificity but low sensitivity. Which statement best describes what this means?
   A. The assay cannot distinguish the drug from like products but cannot detect extremely low concentrations.
   B. The assay cannot distinguish the drug from like products and cannot detect extremely low concentrations.
   C. The assay can distinguish the drug from like products and can detect extremely low concentrations.
   D. The assay can distinguish the drug from like products but cannot detect extremely low concentrations.

C. Assay Terminology
   1. Precision (reproducibility): Closeness of agreement between the results of repeated analyses performed on the same sample
      a. Standard deviation (SD): Average difference of the individual values from the mean
      b. Coefficient of variation (CV): SD as a percentage of the mean (relative rather than absolute variation)

$$\text{CV} = \frac{\text{SD}}{\text{Mean}}$$

   2. Accuracy: Closeness with which a measurement reflects the true value of an object
      • Correlation coefficient: Strength of the relationship between two variables
   3. Predictive performance (measure of accuracy): Precision, expressed as the root mean squared error (RMSE)

$$\text{MSE} = \frac{1}{N}\sum_{i=1}^{N} pe_i^2 \qquad \text{RMSE} = \sqrt{mse}$$

      Bias: a.k.a. mean prediction error (ME)

$$\text{ME} = \frac{1}{N}\sum_{i=1}^{N} pe_i$$

      • Prediction error (*pe*) is the prediction minus the true value.

   4. Sensitivity: Ability of an assay to quantitate low drug concentrations accurately; usually the lowest concentration an assay can differentiate from zero
   5. Specificity (cross-reactivity): Ability of an assay to differentiate the drug in question from like substances

D. Assay Methods
   1. Immunoassays
      a. Radioimmunoassay
         i. Advantages: Extremely sensitive (picogram range)
         ii. Disadvantages: Radioimmunoassay kits have limited shelf life because of the short half-life of labels, radioactive waste, and cross-reactivity.
            • Clinical use for assaying digoxin and cyclosporine
      b. Enzyme immunoassay, e.g., enzyme multiplied immunoassay technique
         i. Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
         ii. Disadvantages: Measuring enzyme activity more complex than radioisotopes, enzyme activity may be affected by plasma constituents, less sensitive than radioimmunoassays

c. Fluorescence immunoassay: TDx (e.g., fluorescence polarization immunoassay): Most common therapeutic drug monitoring assay
   i. Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
   ii. Disadvantages: Background interference attributable to endogenous serum fluorescence

2. Assays used primarily in pharmacokinetic research studies
   a. High-pressure liquid chromatography
   b. Gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry
   c. Flame photometry
   d. Bioassay

E. Population Pharmacokinetics in Therapeutic Drug Monitoring
   1. Population pharmacokinetics useful when
      a. Drug concentrations are obtained during complicated dosing regimens.
      b. Drug concentrations are obtained before steady state.
      c. Only a few drug concentrations are feasibly obtained (limited sampling strategy).
   2. Bayesian pharmacokinetics
      a. Prior population information is combined with patient-specific data to predict the most probable individual parameters.
      b. When patient-specific data are limited, there is greater influence from population parameters; when patient-specific data are extensive, there is less influence.
      c. With a small amount of individual data, Bayesian forecasting generally yields more precise results.

Patient Cases

8. K.M., an 80-year-old white woman (52 kg, 64 inches), is admitted to the hospital for pyelonephritis with sepsis. She has a history of myocardial infarction, heart failure with reduced ejection fraction, hypertension, osteoporosis, rheumatoid arthritis, and cerebrovascular accident. On admission, her BUN is 25 mg/dL, SCr is 0.92 mg/dL, and Alb is 2.9 g/dL. K.M. is initiated on the following drugs: trimethoprim/sulfamethoxazole (240 mg of the trimethoprim component) intravenously every 12 hours, lisinopril 10 mg daily by mouth, digoxin 0.125 mg daily by mouth, furosemide 40 mg daily by mouth, cimetidine 400 mg twice daily by mouth, acetaminophen 650 mg every 6 hours by mouth, calcium carbonate 500 mg three times daily by mouth, and carvedilol 6.25 mg twice daily by mouth. Which is the best assessment of K.M.'s renal function?
   A. Her SCr is in the normal range, and no dosage adjustments are necessary.
   B. Because of her age, K.M. will have some degree of renal dysfunction, and dosages may need to be adjusted.
   C. Because of the pyelonephritis, K.M. will have renal dysfunction, and dosages may need to be adjusted.
   D. Her SCr is in the normal range but her BUN is elevated, so dosages may need to be adjusted.

9. Which of K.M.'s current medications are most likely to alter her SCr concentrations?
   A. Lisinopril and digoxin.
   B. Trimethoprim/sulfamethoxazole and cimetidine.
   C. Furosemide and calcium carbonate.
   D. Acetaminophen and carvedilol.

VIII. PHARMACOKINETICS IN RENAL DISEASE

A. Estimation of Kidney Function Through Glomerular Filtration Rate (GFR) and Creatinine Clearance (CrCl)
   1. Creatinine production and elimination
      a. Creatine is produced in the liver.
      b. Creatinine is the product of creatine metabolism in skeletal muscle, formed at a constant rate for any one person.
      c. Creatinine is filtered at the glomerulus, where it undergoes limited secretion.
      d. CrCl is useful in approximating GFR because:
         i. At normal concentrations of creatinine, secretion is low.
         ii. The creatinine assay picks up a noncreatinine chromogen in the blood but not in the urine.
   2. CrCl calculation to estimate GFR
      • CrCl is calculated from a 24-hour urine collection and the following equation:

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{\text{volume of urine (mL)/1440 minutes} \times \text{urine creatinine concentration (mg/dL)}}{\text{serum creatinine concentration (mg/dL)}}$$

      • Normal CrCl
        Healthy young men = 125 mL/minute/1.73 m^2
        Healthy young women = 115 mL/minute/1.73 m^2
      • After age 30, 1% of GFR is lost per year.
   3. CrCl estimation to estimate GFR
      a. Factors affecting SCr concentrations
         i. Sex
         ii. Age
         iii. Weight and muscle mass
         iv. Renal function. Caveats: CrCl estimations worsen as renal function worsens (usually an overestimation).
      b. Jeliffe

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{98 - 0.8\ (\text{age} - 20)}{\text{SCr}}$$

      Women: Use 90% of the above equation.

      • Limitations
        SCr concentration must be stable.
        Adults 20–80 years of age (equation only applies to this age group)
        Controversy: Rounding up SCr in patients with low concentrations (less than 0.7–1 mg/dL)

      c. Cockcroft-Gault

$$\text{CrCl(mL/min)} = \frac{(140 - \text{Age}) * (\text{weight})}{72 * \text{Scr}}$$

      Women: Use 85% of the above equation.

      • For "weight": Use actual body weight (ABW) in patients with body mass index (BMI) less than 18.5 kg/m^2, ideal body weight (IBW) in patients with BMI 18.5–25 kg/m^2, and IBW plus 40% of (ABW – IBW) in patients with BMI greater than 25 kg/m^2.

        IBW (men) = 50 kg + 2.3 kg for each inch over 5 feet
        IBW (women) = 45.5 kg + 2.3 kg for each inch over 5 feet

- Recommended when making drug dosage adjustments in patients with renal dysfunction, because package insert recommendations generally use this formula to estimate creatinine clearance, and the use of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations to make dosing adjustments has not been validated.

- Limitations
  SCr concentration must be stable.
  Developed for adults only
  Not corrected for creatinine standardization (results in lower estimations)
  Not developed in patients with obesity (see weight recommendations above)

d. Salazar-Corcoran

$$\text{CrCl male (mL/min/1.73 m}^2\text{)} = \frac{(137 - \text{age}) * [(0.285 * \text{weight}) + (12.1 * \text{height}^2)]}{51 * \text{SCr}}$$

$$\text{CrCl female (mL/min/1.73 m}^2\text{)} = \frac{(146 - \text{age}) * [(0.287 * \text{weight}) + (9.74 * \text{height}^2)]}{60 * \text{SCr}}$$

- For "weight": Use actual body weight in kg
- For "height": Use meters
- Used for patients with obesity. No better than using Cockcroft-Gault with appropriate weight adjustments (see above)

e. MDRD study equation

Full equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-0.999} * (\text{age in years})^{-0.176} * 1.180 \text{ (if patient is African American)} * 0.762 \text{ (if patient is a woman)} * (\text{BUN})^{-0.170} * (\text{Alb})^{0.318}$$

Simplified four-variable equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-1.154} * (\text{age in years})^{-0.203} * 1.212 \text{ (if patient is African American)} * 0.742 \text{ (if patient is a woman)}$$

i. These equations directly estimate GFR (*not* CrCl) and were developed using standardized creatinine concentrations to stage kidney function.
ii. These equations are recommended by the American Kidney Foundation and the European Renal Association to estimate renal function.
iii. Not as accurate when GFR is greater than 60 mL/minute/1.73 m^2
iv. If used for drug dosing, convert value from milliliters per minute per 1.73 m^2 to milliliters per minute.
v. If used for drug dosing and significantly different from Cockcroft-Gault, use clinical judgment and optimize risk versus benefit.

f. CKD-Epi equation (Table 10)
i. These equations directly estimate GFR (not CrCl).
ii. These equations are more accurate than MDRD at higher GFRs (i.e., greater than 60 mL/minute/1.73 m^2). CKD-Epi is recommended by KDIGO as the preferred equation for chronic kidney disease staging.

Table 10. Chronic Kidney Disease Epidemiology Collaboration Equation

Race and Sex	Serum Creatinine (mg/dL)	Equation
African American		
Female	< 0.7	$166 * (Scr/0.7)^{-0.329} * (0.993)^{Age}$
	> 0.7	$166 * (Scr/0.7)^{-1.209} * (0.993)^{Age}$
Male	< 0.9	$163 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
	> 0.9	$163 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
White or other		
Female	<0.7	$GFR = 144 * (Scr/0.7)^{-0.329} * (0.993)^{Age}$
	> 0.7	$GFR = 144 * (Scr/0.7)^{-1.209} * (0.993)^{Age}$
Male	< 0.9	$GFR = 141 * (Scr/0.9)^{-0.411} * (0.993)^{Age}$
	> 0.9	$GFR = 141 * (Scr/0.9)^{-1.209} * (0.993)^{Age}$

GFR = glomerular filtration rate; SCr = serum creatinine.

g. Pediatric formulas (Table 11). Do not round up low SCr values in pediatric patients.

Schwartz:

$$GFR\ (mL/minute/1.73\ m^2) = \frac{K * ht\ (cm)}{SCr}$$

Table 11. Schwartz Equation Constants

Age	*K*
Low birth weight ≤ 1 year	0.33
Full term ≤ 1 year	0.45
1–13 years	0.55
13- to 18-year-old adolescent female	0.55
13- to 18-year-old adolescent male	0.7

Note: *K* = 0.413 for 1–13 years old and 13- to 18-year-old adolescent females when using standardized creatinine concentrations (other *K* values have not been updated); this is known as the bedside Chronic Kidney Disease in Children (CKiD) equation.

Counahan-Barratt:

$$GFR\ (mL/minute/1.73\ m^2) = \frac{0.43 * ht\ (cm)}{SCr}$$

4. Factors influencing CrCl estimates
   a. Patient characteristics
      i. Age (↓ production of creatinine with age)
      ii. Female sex (↓ production of creatinine)
      iii. Race (↑ production of creatinine in African Americans)
   b. Disease states and clinical conditions
      i. Spinal cord injuries (↓ muscle mass; ↓ creatinine)
      ii. Amputations (↓ muscle mass; ↓ creatinine)
      iii. Cushing syndrome (↓ muscle mass; ↓ creatinine)
      iv. Muscular dystrophy (↓ muscle mass; ↓ creatinine)
      v. Guillain-Barré syndrome (↓ muscle mass; ↓ creatinine)
      vi. Rheumatoid arthritis (↓ muscle mass; ↓ creatinine)
      vii. Liver disease (↓ creatine; ↓ creatinine)
      viii. Glomerulopathic disease (greater amount of creatinine secretion in relation to filtration)
      ix. Hydration status (dehydration vs. fluid overload)

c. Diet
   i. High-meat protein diets (↑ creatinine ingestion)
   ii. Vegetarians (↓ creatinine ingestion)
   iii. Protein calorie malnutrition (↓ creatinine ingestion)
d. Drugs and endogenous substances
   i. Laboratory interaction: Kinetic alkaline picrate method
      (a) Noncreatinine chromogens: In blood but not in urine
      (b) Cephalosporins (especially cefoxitin): Chromogenic, causing false elevations that are much greater in urine than in blood
      (c) Acetoacetate (elevated in fasting patients, patients with diabetic ketoacidosis): Chromogenic, causing false elevations
   ii. Pharmacokinetic interaction: Drugs compete with creatinine for renal secretion (causing false elevations), cobicistat, trimethoprim, cimetidine, fibric acid derivatives (other than gemfibrozil), and dronedarone.

B. Drug Dosing in Renal Disease
1. Loading dose
   a. In general, no alteration is necessary, but it should be given to hasten the achievement of therapeutic drug concentrations.
   b. Alterations in loading dose must occur if the Vd is altered secondary to renal dysfunction. Example: Decrease digoxin loading doses in renal disease because of a decreased Vd.
2. Maintenance dosage: Alterations should be made in either the dosage or the dosing interval.
   a. Changing the dosing interval
      i. Use when the goal is to achieve similar steady-state concentrations.
      ii. Less costly
      iii. Ideal for limited-dosage forms (i.e., oral medications)
   b. Changing the dosage
      i. Use when the goal is to maintain a steady therapeutic concentration.
      ii. More costly
   c. Changing the dosage and the dosing interval
      i. Often necessary for substantial dosage adjustment with limited-dosage forms
      ii. Often necessary for narrow therapeutic index drugs with target concentrations
         (a) If a drug is given more than once daily, then adjust the interval.
         (b) If a drug is given once daily or less often, then adjust the dosage.
   d. Augmented renal clearance
      i. Increased creatinine clearance in critically ill patients, resulting in greater elimination of renally eliminated drugs
      ii. Most common in patients with severe neurologic injury, sepsis, trauma, or burns
      iii. Associated with subtherapeutic concentrations of antibiotics, especially β-lactams and vancomycin

Patient Case

10. S.J. is a 55-year-old man with hepatic dysfunction and an anaerobic infection caused by Prevotella spp. He has a small amount of ascites but is not encephalopathic. He is initiated on metronidazole, and the package insert states that dosages should be decreased by 50% in patients with a Child-Pugh score greater than 9. If he has the following hepatic laboratory values, which best estimates his Child-Pugh score?

Patient Case (*Cont'd*)

Aspartate transaminase = 85 U/L, alanine transaminase = 56 U/L, alkaline phosphatase = 190 U/L, total bilirubin = 1.8 mg/dL, Alb = 2.9 g/dL, lactic dehydrogenase = 270 U/L, prothrombin time/international normalized ratio = 14.6/1.7, γ-glutamyl transferase = 60 U/L

A. 3.

B. 5.

C. 8.

D. 11.

IX. PHARMACOKINETICS IN HEPATIC DISEASE

A. Dosage Adjustment in Hepatic Disease
   1. Clinical response is the most important factor in adjusting dosages in hepatic disease.
   2. Low–hepatic extraction ratio drugs
      a. Adjustment of maintenance dosage is necessary only when hepatic disease alters the intrinsic clearance (Cl_{int}).
      b. Alterations in protein binding alone do not require alteration of maintenance dosage, even though total drug concentrations decline.
      c. Loading doses may require reduction.
      d. Examples: carbamazepine, diazepam, phenytoin, warfarin
   3. High–hepatic extraction ratio drugs
      a. Intravenous administration
         i. Usually necessary to decrease maintenance dose rate as hepatic blood flow changes
         ii. Consider effect of hepatic disease on protein binding as it alters free concentrations.
      b. Oral administration: Similar to low–hepatic extraction ratio drugs; necessary to decrease maintenance dose rate when hepatic disease alters Cl_{int}
      c. Examples: haloperidol, morphine, metoprolol, propranolol, verapamil

B. Rules for Dosing in Hepatic Disease
   1. Hepatic elimination of high–extraction ratio drugs is more consistently affected by liver disease than hepatic elimination of low–extraction ratio drugs.
   2. The clearance of drugs that are exclusively conjugated is not substantially altered in liver disease.
   3. Adjustments for some drugs based on Child-Pugh scores (Table 12).

Table 12. Child-Pugh Classification for Liver Disease

	Points		
	1	**2**	**3**
Encephalopathy	0	1 or 2	3 or 4
Ascites	0	+	++
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds over control) or INR (values in brackets)	0–4 [< 1.7]	4–6 [1.7–2.3]	> 6 [> 2.3]

Pugh score: 5 = normal; 6 or 7 = mild (A); 8 or 9 = moderate (B); >9 = severe (C).

X. PHARMACODYNAMICS

Patient Case

11. Which is the most likely reason that a drug will follow clockwise hysteresis?
    A. Formation of an active metabolite.
    B. Delay in equilibrium between the blood and the site of action.
    C. Tolerance.
    D. Increased sensitivity with time.

A. Definition: Relationship Between Drug Concentrations and the Pharmacologic Response

B. Hill equation

$$E = \frac{E_{max} * C^{y}}{EC_{50}^{y} + C^{y}}$$

E = pharmacologic response
E_{max} = maximum drug effect
EC_{50} = concentration producing half of the maximum drug effect
γ = Hill coefficient that accommodates the shape of the curve

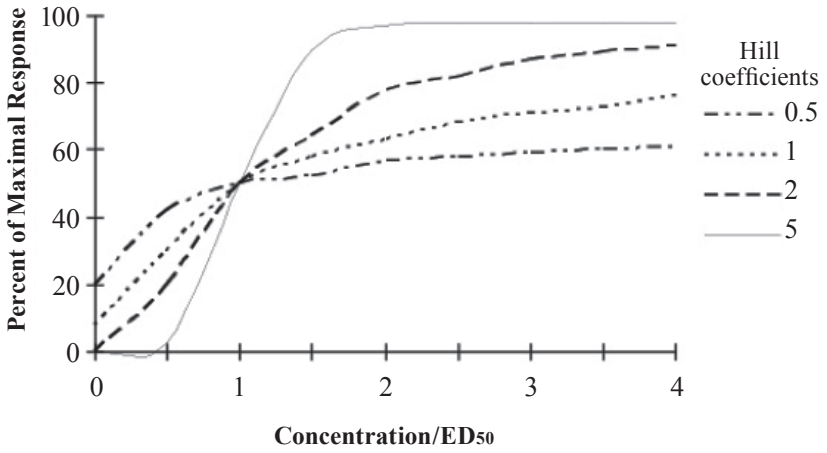

Figure 5. Concentration response plot.

C. Hysteresis Loops. Definition: Concentrations late after a dose produce an effect different from that produced by the same concentration soon after the dose.

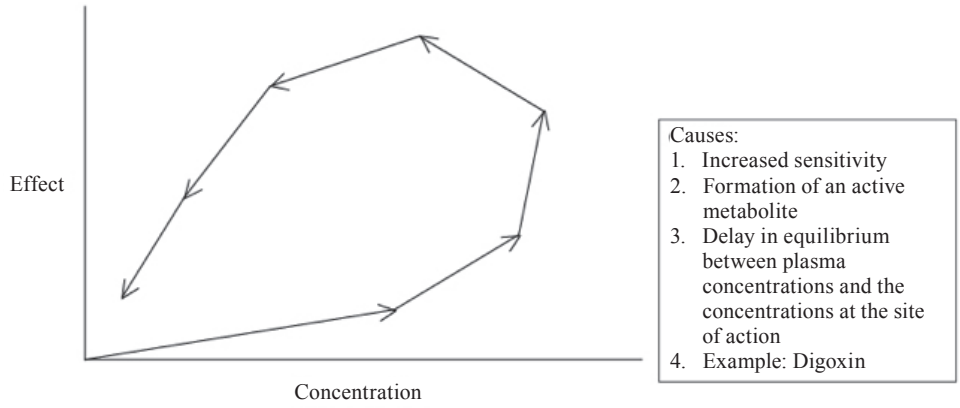
Effect
Concentration
Causes:
1. Increased sensitivity
2. Formation of an active metabolite
3. Delay in equilibrium between plasma concentrations and the concentrations at the site of action
4. Example: Digoxin

Figure 6. Counterclockwise hysteresis.

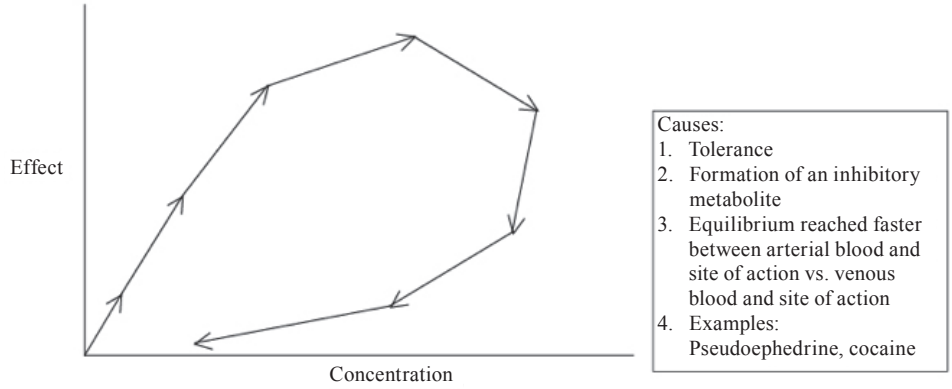
Effect
Concentration
Causes:
1. Tolerance
2. Formation of an inhibitory metabolite
3. Equilibrium reached faster between arterial blood and site of action vs. venous blood and site of action
4. Examples: Pseudoephedrine, cocaine

Figure 7. Clockwise hysteresis.

Patient Cases

12. P.L., a 45-year-old man with end-stage renal disease on dialysis is receiving phenytoin 400 mg/day for a history of tonic-clonic seizures. His phenytoin concentration today is 13.6 mg/L, and his Alb concentration is 4.2 g/dL. Given his current concentrations, which change would best be recommended?
    A. Make no changes to his drug regimen.
    B. Keep the total daily dosage the same, but change the regimen to 200 mg two times/day.
    C. Increase the dosage for better seizure control.
    D. Decrease the dosage to prevent toxicity.

13. N.R. is a 63-year-old man with renal insufficiency who comes to the emergency department in atrial fibrillation with a ventricular rate of 120 beats/minute. Because of significant hypotension, it is decided to initiate him on digoxin for rate control. Which is the best dosing for this patient?
    A. The loading dose should remain the same, but the maintenance dose should be decreased.
    B. The loading dose should be decreased, and the maintenance dose should remain the same.
    C. Neither the loading dose nor the maintenance dose should be adjusted.
    D. Both the loading dose and the maintenance dose should be decreased.

14. P.P. is a 34-year-old man with a history of cerebral palsy and chronic urinary tract infections. He is admitted to the hospital with a *Pseudomonas* urinary tract infection that is resistant to all antibiotics except for aminoglycosides. He is initiated on once-daily tobramycin at 400 mg/day intravenously. Which statement best describes this high-dose, extended-interval aminoglycoside regimen?
    A. It takes advantage of the concentration-dependent killing of aminoglycosides.
    B. It is more efficacious than standard aminoglycoside dosing.
    C. It does not require the monitoring of aminoglycoside concentrations.
    D. It will not cause nephrotoxicity.

XI. THERAPEUTIC DRUG MONITORING (Table 13)

Table 13. Therapeutic Drug Monitoring of Specific Drugs

Drug	Therapeutic Range	Sampling Issues	Comments
Aminoglycosides	Peak = 4–10 mg/L maximum Amikacin = 20–30 mg/L Trough < 2 mg/L minimum Amikacin < 10 mg/L Higher maximum concentrations for high-dose extended-interval dosing	Duration of infusion, timing of first sample after infusion (generally should be ½–1 hour)	High-dose extended-interval ("once-daily") aminoglycoside dosing is generally recommended to decrease toxicity and improve efficacy These regimens are just as effective as traditional dosing, and meta-analyses have demonstrated less nephrotoxicity or no difference
Vancomycin	Bayesian-derived AUC/MIC ratio of 400–600	AUC derived by (1) collecting two concentrations (a near steady-state, post-distributional Cmax at 1–2 hr post-infusion, and a trough) during the same dosing interval and using first-order PK equations to estimate the AUC or (2) collecting one or two concentrations (at least one trough) and using Bayesian software programs to estimate the AUC	Trough-only monitoring of vancomycin is no longer recommended for serious methicillin-resistant Staphylococcus aureus infections, and clinical PK services should move to AUC/MIC monitoring. If an MIC is not available, assume 1 mg/L. Loading doses are recommended for ICU patients, those receiving renal replacement therapy, and those receiving continuous infusions
Phenytoin/ Fosphenytoin	10–20 mg/L Free: 1–2 mg/L	In general, obtain trough concentrations	Percentage free increases with renal failure and hypoalbuminemia Equations to correct: Changes in albumin: $Cp = \frac{Cp'}{(0.9 * \frac{Alb}{4.4}) + 0.1}$ Renal failure: $Cp = \frac{Cp'}{0.5}$ Renal failure with change in albumin: $Cp = \frac{Cp'}{(0.48 * 0.9 * \frac{Alb}{4.4}) + 0.1}$ Enzyme inducer; susceptible to metabolic drug interactions
Carbamazepine	4–12 mg/L		Enzyme inducer/autoinduction; active metabolite 10,11 epoxide
Phenobarbital	15–40 mg/L		Enzyme inducer
Valproic acid	50–100 mg/L		Saturable protein binding; percentage free increases with renal failure and hypoalbuminemia
Digoxin	0.8–2 mcg/L	Prolonged distribution period necessitates sampling > 6–12 hours after dose	Volume of distribution decreases in renal disease; susceptible to drug interactions
Cyclosporine	100–250 mcg/L	Whole blood samples	Many drug interactions
Lithium	0.3–1.3 mmol/L	Prolonged distribution necessitates sampling 12 hours after dose	
Theophylline	10–20 mg/L		Treat as continuous infusion with sustained-release dosage forms

Cp = concentration of drug in plasma; Vd.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C
In 6 days (2 half-lives), the concentration will decrease from 41.9 mg/L to about 10.5 mg/L; now is the time to redose (Answer C is correct). A 1-g dose given on March 24 will increase the concentration in the blood from 14.1 mg/L to 41.9 mg/L (14.1 + 27.8 mg/L). Given that the half-life is about 3 days, it will take longer than 1 day to reach a concentration of about 10 mg/L (Answer A is incorrect). In 3 days (1 half-life), the concentration will decrease from 41.9 mg/L to about 21 mg/L—still too early to redose (Answer B is incorrect). Redosing can be determined because plenty of information exists about how to calculate when to redose (Answer D is incorrect).

2. Answer: A
F = (100 mg * 25 mg*hr/L)/(200 mg * 50 mg*hr/L) = 25% (Answer A is correct). (Answers B, C, and D are all incorrect).

3. Answer: D
P-glycoprotein is an efflux pump that pumps drugs back into the GI lumen (Answer D is correct). P-glycoprotein is not a plasma protein (Answer A is incorrect), and it does not transfer drugs through the GI mucosa (Answer B is incorrect); rather, it pumps drugs back into the GI lumen. In addition, P-glycoprotein acts in concert with CYP3A4 to diminish oral absorption (Answer C is incorrect).

4. Answer: C
Azithromycin does not inhibit CYP3A4 (Answer C is correct). Erythromycin and clarithromycin are potent inhibitors of CYP3A4 and would be expected to increase cyclosporine concentrations (Answers A and B are incorrect). Although doxycycline would not interact, it should not be chosen because azithromycin is an option (Answer D is incorrect).

5. Answer: B
Clopidogrel is a prodrug. Therefore, to be effective, it must be metabolized into the active form. Because this metabolism is primarily performed by CYP2C19 and this patient is a CYP2C19 poor metabolizer, he will not produce as much active drug, increasing the risk of a thrombotic event (Answer B is correct). The clopidogrel metabolite formed does not block the action of aspirin (Answer A is incorrect). Because the clopidogrel metabolite is the active form of the medication, slowing metabolism will not increase bleeding, but instead will have the opposite effect (Answer C is incorrect). Because he is a slow metabolizer of CYP2C19, he will not overproduce the active metabolite (Answer D is incorrect).

6. Answer: B
By definition, clearance becomes nonlinear once the concentration exceeds the K_m (Answer A is incorrect); therefore, the concentrations will more than double (Answer B is correct). Phenytoin is not a significant autoinducer (Answer C is incorrect). Although phenytoin absorption decreases as the dosage is increased, it is not clinically significant until a single dose exceeds 400 mg (Answer D is incorrect).

7. Answer: D
The correct answer is that the assay will be able to distinguish the drug from like products but will not be able to detect extremely low concentrations (Answer D is correct). High specificity means the assay can distinguish the drug from like products (Answers A and B are incorrect), and low sensitivity means the assay cannot detect extremely low concentrations (Answer C is incorrect).

8. Answer: B
Although her SCr is in the normal range, her renal function is decreased because of her age (Answer A is incorrect). After age 30, patients lose around 1 mL/minute/year of CrCl. Therefore, her CrCl needs to be calculated to assess drug dosing (Answer B is correct). Patients with pyelonephritis do not have a decrease in their renal function (Answer C is incorrect). Her elevated BUN is probably a sign of prerenal azotemia caused by dehydration associated with her infection. The BUN measurement is generally not used to assess renal function for drug dosing purposes (Answer D is incorrect).

9. Answer: B

Both trimethoprim/sulfamethoxazole and cimetidine compete with creatinine for secretion in the kidneys, increasing SCr concentrations (Answer B is correct). Although angiotensin-converting enzyme inhibitors may transiently increase SCr concentrations, digoxin does not affect renal function (Answer A is incorrect). Although furosemide may secondarily affect SCr concentrations, calcium carbonate does not affect renal function (Answer C is incorrect). Acetaminophen and carvedilol generally do not affect SCr concentrations (Answer D is incorrect).

10. Answer: C

This patient has 1 point for not being encephalopathic, 2 points for mild ascites, 1 point for the bilirubin concentration, 2 points for the albumin concentration, and 2 points for the INR, for a total of 8 points (Answer C is correct). Normal patients have a Child-Pugh score of 5, which means no hepatic dysfunction (Answers A, B, and D are incorrect).

11. Answer: C

Tolerance leads to a decrease in effect with time; this is clockwise hysteresis (Answer C is correct). The formation of an active metabolite, a delay in equilibrium between the blood and the site of action, and the increased sensitivity with time would lead to an increase in effect with time; this is counterclockwise hysteresis (Answers A, B, and D are all incorrect).

12. Answer: D

The dosage should be decreased to prevent toxicity (Answer D is correct). In renal failure, acidic byproducts build up in the blood and compete with phenytoin for protein binding. Total concentrations must be corrected, and this correction leads to a doubling of the concentration. Therefore, the current concentration is too high, and the dosage should be decreased (Answers A and C are incorrect). Single doses of 400 mg are fine (doses higher than 400 mg should be divided) (Answer B is incorrect).

13. Answer: D

Both the loading dose and the maintenance dose should be decreased (Answer D is correct). In general, loading doses need not be altered in renal dysfunction because they primarily depend on the Vd. However, the digoxin Vd is decreased in renal dysfunction (Answers A and C are incorrect). Because digoxin is eliminated renally, the maintenance dose should be decreased (Answers B and C are incorrect).

14. Answer: A

Aminoglycosides have concentration-dependent killing, and a high-dose, extended-interval aminoglycoside regimen takes advantage of this characteristic (Answer A is correct). However, it has not proved more efficacious than traditional dosing (Answer B is incorrect). Aminoglycoside concentrations still need to be monitored with high-dose, extended-interval therapy (Answer C is incorrect). In addition, high-dose, extended-interval aminoglycoside dosing can still cause nephrotoxicity (although the incidence is generally diminished) (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
With two concentrations, data are sufficient to calculate an elimination rate constant and, therefore, a half-life (Answers C and D are incorrect; Answer B is correct). In addition, the Vd can be calculated by back extrapolation to the Cmax and use of appropriate equations (because this was the first dose, and therefore it is known that the tobramycin concentration was 0 mg/L before the dose was given) (Answer A is incorrect and Answer B is correct).

2. Answer: A
The elimination rate constant equals (ln 3.6 mg/L − ln 0.9 mg/L)/4 hours = 0.35/hour. The half-life is 0.693/0.35 = 2 hours. The concentration at the end of the infusion equals 3.6 mg/L/e – (0.35 * 1) = 5.1 mg/L. The patient's Vd = dose/change in concentration, or 110 mg/5.1 mg/L = 21.5 L (Answer A is correct; Answers B, C, and D are all incorrect).

3. Answer: B
Her clearance increased because of the improvement in renal function, which increased her elimination rate constant and decreased her half-life (Answer B is correct). The Vd would not be altered by changes in clearance (they are independent) (Answer A is incorrect). With the diuresis and angiotensin-converting enzyme inhibitor, her Vd probably decreased, but clearance would not be altered by changes in Vd (they are independent) (Answer C is incorrect). In addition, if her Vd decreased, her half-life would decrease, not increase (Answer D is incorrect).

4. Answer: C
Because the trough and AUC/MIC are too low, the interval will have to be shortened to increase the concentration (Answers A and B are incorrect). Maintaining the total daily dose will not increase the AUC/MIC to the appropriate range (Answer D is incorrect). Vancomycin largely follows linear pharmacokinetics. In the absence of changes to clearance and volume, doubling the dose in a 24-hour period will double the exposure (AUC). Therefore, increasing from 1000 mg daily to 1000 mg every 12 hours will increase the AUC/MIC from 210 to 420 (Answer C is correct).

5. Answer: B
To achieve flucytosine peak concentrations of 50–100 mg/L. (assuming a trough concentration of 25 mg/L, dosing every 6 hours, and 100% bioavailability; flucytosine volume of distribution of 0.7 L/kg; half-life of 3 hours), the concentration must be changed by 25–75 mg/L. Using the equation ΔCp = dose/Vd, a dosage of 12.5 mg/kg would increase the concentration by only 17.8 mg/L. A dosage of 75 mg/kg would increase the concentration by 107 mg/L., whereas a dosage of 150 mg/kg would increase the concentration by 214 mg/L. The correct dosage is 37.5 mg/kg because it would increase the concentration by 53.6 mg/L. (Answer B is correct; Answers A, C, and D are all incorrect).

6. Answer: D
Because of the patient's renal failure and low Alb, the total concentration must be corrected. The patient's corrected phenytoin concentration is 14.9 mg/L (Cp = 5.6/ {[0.48 x 0.9 x (2.8/4.4)] + 0.1} = 14.9 mg/L). Therefore, no changes should be made to the dosage (Answer D is correct; Answers A, B, and C are all incorrect).

7. Answer: C
Both of these are immunoassays but they are different (Answer D is incorrect). Because they are both immunoassays, they both use antibodies to bind the molecule of interest (Answer A is incorrect). A brand name for the Abbott fluorescence polarization immunoassay is TDx, which uses a fluorescent label. The term *EMIT* stands for *enzyme multiplied immunoassay technique,* which is an immunoassay that uses an enzyme label (Answer C is correct). Neither of them use radioisotopes (Answer B is incorrect).

8. Answer: D
The digoxin concentration was obtained too close to the 8:00 a.m. dose. The digoxin had not yet had a chance to complete its distribution phase. Once distribution is complete (generally 6–12 hours after the dose), the concentration will be lower and probably within the therapeutic range (Answer D is correct). Therefore, there is no need for the digoxin antibody (Answer A is incorrect), activated charcoal (Answer C is incorrect), or lowering of the dosage (Answer B is incorrect).

9. Answer: C

The correct statistical test is multiple regression. Multiple regression is used to describe the relationship between a dependent variable and two or more independent variables when both the dependent and independent variables are numeric (Answer C is correct). Analysis of variance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal (Answer A is incorrect). Likewise, analysis of covariance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal with confounding factors (Answer B is incorrect). Spearman rank correlation is a nonparametric test used to describe the relationship between one dependent and one independent variable when the data are ordinal or numeric and not normally distributed (Answer D is incorrect).

10. Answer: B

Assessing adherence and increasing her dosage is the best recommendation, because the concentration is below the therapeutic range (Answer B is correct). The valproic acid therapeutic range is 50–100 mg/L, and she is well below this concentration. Although some patients are controlled at lower concentrations, this concentration is probably too low (Answer A is incorrect). She definitely does not need a decrease in dosage (Answer C is incorrect). Although total valproic acid concentrations are affected by changes in Alb, her Alb is normal, and obtaining a free concentration is unnecessary (Answer D is incorrect).

11. Answer: B

Codeine's activity is due primarily to its metabolism to morphine by CYP2D6 after administration. Because this patient is a CYP2D6 poor metabolizer, less of the codeine will be metabolized to its active metabolite (Answer B is correct and Answer C is incorrect). Omeprazole does inhibit CYP2C19, but this enzyme does not metabolize codeine (Answer A is incorrect). Metoprolol is a substrate of CYP2D6 but is not an inhibitor or inducer of CYP2C9 (Answer D is incorrect).

12. Answer: D

The MDRD and CKD-Epi are actually better estimates of renal function because they directly estimate GFR instead of CrCl (Answer A is incorrect). Although the Cockcroft-Gault equation was developed in hospitalized patients and the MDRD and CKD-Epi equations were developed in ambulatory patients, this does not impact the setting where they can be used (Answer B is incorrect). Moreover, although the equations do have different units (mL/minute vs. mL/minute/1.73 m^2), this can easily be corrected by converting the result of the MDRD or CKD-Epi equation to milliliters per minute (Answer C is incorrect). The best reason for not using MDRD or CKD-Epi for drug dosing is that renal dosing adjustment recommendations published in package inserts are almost always based on CrCl estimates using the Cockcroft-Gault equation (Answer D is correct).

13. Answer: A

Assays with low sensitivity will not be able to detect low drug concentrations, which may still be therapeutic (Answer A is correct). Assays that cannot differentiate between like substances have low specificity (Answers C and D are incorrect). Assays that report highly variable values when repeatedly run on the same sample have low precision (Answer A is correct). Assays that consistently over- or under-predict the true concentration have low accuracy (Answers B and C are incorrect).

Gastrointestinal Disorders

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Gastrointestinal Disorders

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Learning Objectives

1. Review national guideline treatment strategies for the following gastrointestinal (GI) disorders: gastroesophageal reflux disease (GERD); peptic ulcer disease (PUD); ulcerative colitis (UC); Crohn disease (CD); chronic liver disease, including viral hepatitis and cirrhosis; constipation; diarrhea; irritable bowel syndrome (IBS); nausea; vomiting; pancreatitis; and upper GI bleeding, including prevention of stress-related mucosal disease (SRMD).
2. Recommend appropriate pharmacologic and nonpharmacologic interventions given a specific patient with one or more GI disorders.
3. Recognize pertinent information for educating patients and prescribers regarding the appropriate use of pharmacologic agents for various GI disorders.
4. Apply evidence related to GI disorders for patient care, including appropriate interpretation or use of study designs and statistical tests.

Abbreviations in This Chapter

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	Crohn disease
COX-2	cyclooxygenase-2
CV	cardiovascular
GFR	glomerular filtration rate
GI	gastrointestinal
HAV	hepatitis A virus
HCP	health care provider
HCV	hepatitis C virus
H_2RA	histamine-2 receptor antagonist
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
INR	international normalized ratio
MDF	Maddrey discriminant function
MELD	model for end-stage liver disease
NG	nasogastric
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PPI	proton pump inhibitor
PUD	peptic ulcer disease
SBP	spontaneous bacterial peritonitis
SCr	serum creatinine
TNF	tumor necrosis factor
UBT	urea breath test
UC	ulcerative colitis

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. A 58-year-old African American man presents with a 2-month history of burning epigastric pain and intermittent difficulty swallowing. The pain is not relieved by positional changes or eating, and he has tried calcium carbonate (500 mg) chewable tablets when symptoms occur, resulting in minimal relief. He takes amlodipine 5 mg/day for hypertension and ibuprofen for occasional back pain. Which action is best for this patient?
   A. Initiate famotidine 20 mg/day.
   B. Refer for possible endoscopic evaluation.
   C. Initiate omeprazole 20 mg twice daily.
   D. Change amlodipine to hydrochlorothiazide.

2. A 50-year-old woman is seen in the clinic for severe pain related to the swelling of three of her metacarpophalangeal joints on each hand and swelling of her right wrist. She cannot write or perform her usual household activities. Radiograms of these joints reveal bony decalcifications and erosions. A serum rheumatoid factor is obtained, which is elevated. Her medical history includes type 2 diabetes, hypertension, and dyslipidemia. Her medications include metformin 1000 mg twice daily, glyburide 10 mg/day, metoprolol 100 mg twice daily, aspirin 81 mg/day, and rosuvastatin 5 mg/day. The primary care provider would like to initiate systemic anti-inflammatory therapy for this patient's rheumatoid arthritis with high-dose nonsteroidal anti-inflammatory drug (NSAID) therapy; however, the primary care provider is worried about potential gastrointestinal (GI) toxicity. What is the best regimen for treating this patient's pain while minimizing the risk of GI toxicity?
   A. Celecoxib 400 mg twice daily.
   B. Indomethacin 75 mg/day plus famotidine 10 mg/day.

C. Naproxen 500 mg twice daily plus omeprazole 20 mg/day.

D. Piroxicam 20 mg/day plus misoprostol 600 mcg three times daily.

3. A 68-year-old Hispanic man is assessed in the emergency department for a 36-hour history of black, tarry stools; dizziness; confusion; and vomiting a substance resembling coffee grounds. He has a medical history of osteoarthritis, hypertension, myocardial infarction (MI) in 2009 and 2011, and seasonal allergies. He has taken naproxen 500 mg twice daily for 4 years, metoprolol 100 mg twice daily, aspirin 325 mg/day, and loratadine 10 mg/day. Nasogastric (NG) aspiration is positive for blood, and subsequent endoscopy reveals a 3-cm antral ulcer with a visible vessel. The vessel is obliterated using an epinephrine solution, and a rapid urease test is negative for *Helicobacter pylori*. Which recommendation is best for this patient?

   A. Intravenous famotidine 20 mg twice daily for 5 days.

   B. Sucralfate 1 g four times daily by NG tube.

   C. Oral lansoprazole 15 mg/day by NG tube.

   D. Pantoprazole 80 mg intravenous bolus, followed by an 8-mg/hour infusion.

4. A 38-year-old woman presents with an 8-week history of new-onset cramping abdominal pain together with 2–4 bloody stools per day. The patient does not have tachycardia or fever. She has a medical history of urinary tract infection and reports an allergy to "sulfa"-containing medications (shortness of breath). Colonoscopy reveals diffuse superficial colonic inflammation consistent with ulcerative colitis (UC). The inflammation is continuous and extends to the hepatic flexure. Which drug therapy is best?

   A. Sulfasalazine extended release tablets 1 g orally three times daily.

   B. Hydrocortisone enema 100 mg every night.

   C. Mercaptopurine 75 mg orally once daily.

   D. Mesalamine (Delzicol) 800 mg orally three times daily.

5. A 45-year-old African American man with a history of alcoholic cirrhosis (Child-Pugh class B) was seen in the clinic for a follow-up. He was recently referred for a screening endoscopy, which revealed several large esophageal varices. He has no history of bleeding; 1 month ago, propranolol 10 mg orally three times daily was initiated. At that time, his vital signs included body temperature 98.7°F (37°C), heart rate 85 beats/minute, respiratory rate 15 breaths/minute, and blood pressure 130/80 mm Hg. At his evaluation today, he seems to be tolerating the propranolol dose and has no new concerns. His vital signs now include body temperature 98.6°F, heart rate 79 beats/minute, respiratory rate 14 breaths/minute, and blood pressure 128/78 mm Hg. What is the best course of action?

   A. Continue current therapy, with a close follow-up in 4 weeks.

   B. Increase propranolol to 20 mg orally three times daily.

   C. Add isosorbide dinitrate 10 mg orally three times daily.

   D. Change propranolol to atenolol 25 mg orally once daily.

6. A new stool antigen test to detect *H. pylori* was tested in 1000 patients with suspected peptic ulcer disease (PUD), and 865 had a positive result. All patients had also undergone a concomitant endoscopy with biopsy and culture as the gold standard comparative test, and 900 had a positive result. Of these 900 patients with confirmed disease, only 850 also had a positive result with the new stool antigen test. From these results, which best represents the sensitivity and specificity of the new stool antigen test?

   A. Sensitivity 82%, specificity 86%.

   B. Sensitivity 85%, specificity 97%.

   C. Sensitivity 94%, specificity 85%.

   D. Sensitivity 96%, specificity 90%.

7. A 50-year-old Asian woman is seeking advice regarding a recent possible exposure to hepatitis A virus (HAV). She saw on the local news report that a chef at a local restaurant where she had eaten about 3 weeks earlier had active HAV. Having

heard that HAV could be transmitted through food, she would like to know her options. She has not previously received the HAV vaccine. Which is the best recommendation for this patient?

A. Initiate HAV vaccine.
B. Administer HAV immune globulin.
C. Continue to observe the patient for symptoms.
D. Initiate HAV vaccine and immune globulin.

8. A 48-year-old woman is admitted to the general medicine floor with abdominal pain, severe nausea and vomiting, and abdominal distension secondary to alcoholic hepatitis. She has a history of alcohol abuse for 20 years and takes no current medications. Her serum creatinine (SCr) is 0.5 mg/dL, aspartate aminotransferase (AST) 250 IU/L, alanine aminotransferase (ALT) 60 IU/L, total bilirubin 10.3 mg/dL, prothrombin time 19 seconds (control 12 seconds), and albumin 2.1 g/L. An abdominal paracentesis shows no evidence of spontaneous bacterial peritonitis (SBP). She reports no known drug allergies. What is the treatment for this patient's alcoholic hepatitis?

A. Naproxen 220 mg orally twice daily.
B. Octreotide 50 mcg/hour intravenously.
C. Prednisolone 40 mg/day.
D. Midodrine 7.5 mg three times daily.

9. A 50-year-old man (weight 80 kg) with a history of intravenous drug abuse and chronic hepatitis C virus (HCV; genotype 3 with compensated cirrhosis and NS5A resistance-associated substitutions present) started taking sofosbuvir 400 mg/velpatasvir 100 mg daily and ribavirin 600 mg orally twice daily 2 weeks ago. He returns to the clinic today with fatigue, scleral icterus, and pallor. There is no clinical evidence of bleeding. Laboratory values reveal the following: hematocrit 31% (baseline 39%), total bilirubin 3.2 mg/dL (indirect 2.7 mg/dL, direct 0.5 mg/dL), AST 150 IU/mL (baseline 300 IU/mL), ALT 180 IU/mL (baseline 400 IU/mL), SCr 0.7 mg/dL, HCV RNA 1×10^6 IU/mL (baseline 2.3×10^6 copies/mL), white blood cell count (WBC) 7.8×10^3 cells/mm^3, and platelet count 160,000/mm^3. What is the most likely cause of this patient's current symptoms?

A. Worsening of his liver disease secondary to inadequate treatment.
B. An adverse effect secondary to treatment with sofosbuvir.
C. Systemic manifestations of chronic HCV disease.
D. An adverse effect secondary to treatment with ribavirin.

10. A 35-year-old man with a history of Crohn disease (CD) is in the clinic today with a chief concern of mucopurulent drainage from an erythematous region on his abdomen. Examination reveals a moderate-size enterocutaneous fistula in the left upper abdominal area. He takes mesalamine (Pentasa) 250 mg in four capsules three times daily and azathioprine 150 mg/day. His physician wants to prescribe infliximab. Which recommendation is best when initiating infliximab therapy?

A. Rule out tuberculosis by purified protein derivative or QuantiFERON-TB test.
B. Administer a test dose before the initial infusion.
C. Admit the patient to the hospital for the administration of all doses.
D. Obtain an echocardiogram to assess cardiac function.

11. A 41-year-old woman (height 65 inches, weight 70 kg) with a history of bipolar disorder and recurrent urinary tract infections is admitted to the general medicine service with severe nausea, vomiting, fever, and back pain. On examination, she has fever, dry mucous membranes, and right-sided costovertebral tenderness. A urinalysis, which reveals many bacteria, is positive for leukocyte esterase. Her SCr is 1.3 mg/dL, and blood urea nitrogen (BUN) is 29 mg/dL. She takes risperidone 6 mg twice daily and sertraline 150 mg/day. She reports an allergy to trimethoprim/sulfamethoxazole that causes a rash. Which drug would be best for treating this patient's nausea?

A. Prochlorperazine 10-mg tablet orally twice daily.
B. Metoclopramide orally disintegrating tablets (ODTs) 5 mg three times daily.

C. Ondansetron 4 mg intravenously three or four times daily.

D. Diphenhydramine 50 mg intravenously three or four times daily.

12. A 75-year-old man (height 58 inches, weight 68 kg) with a history of hypertension, type 2 diabetes, and chronic low back pain is admitted to the hospital for abdominal pain lasting 2 days. He denies fever, chills, or sick contacts. His last bowel movement was 3–4 days ago. On examination, he is afebrile and has moderate left upper and lower quadrant tenderness. An abdominal radiograph reveals large amounts of stool in the colon with no signs of obstruction. He currently takes lisinopril 20 mg/day, verapamil 240 mg once daily, acetaminophen 500 mg four times daily, oxycodone sustained release 20 mg twice daily, and oxycodone/acetaminophen 5/325 mg as needed for pain. His SCr is 1.8 mg/dL (baseline 1.7 mg/dL). Which therapy would best manage this patient's constipation?

A. Sodium phosphate oral solution.

B. Bisacodyl suppository.

C. Methylcellulose tablets.

D. Methylnaltrexone injection.

13. A 65-year-old man (height 68 inches, weight 79 kg) with a history of hypothyroidism, heart failure, and MI is admitted to the intensive care unit with severe community-acquired pneumonia. Six hours after admission, he develops acute respiratory failure, hypotension, and acute kidney injury from presumed sepsis. Mechanical ventilation is implemented, and an NG tube is placed. He currently takes ramipril 10 mg/day, metoprolol 100 mg twice daily, levothyroxine 125 mcg/day, and aspirin 81 mg/day. His WBC is 25×10^3 cells/mm^3, platelet count is 170,000/mm^3, SCr is 3.8 mg/dL (baseline 1.1 mg/dL), potassium is 4.9 mEq/L, BUN is 65 mg/dL, international normalized ratio (INR) is 1.1, AST is 30 IU/mL, and ALT is 45 IU/mL. Which approach is most appropriate for preventing stress-related mucosal disease (SRMD) in this patient?

A. Sucralfate 1 g four times daily by NG tube.

B. Magnesium hydroxide 30 mL four times daily by NG tube.

C. Cimetidine 8-mg/hour intravenous infusion.

D. Pantoprazole 40 mg intravenously once daily.

14. A newly available NSAID was designed to reduce the incidence of adverse GI events compared with traditional NSAIDs. A large retrospective cohort study compares the incidence of ulceration and bleeding associated with the use of this new NSAID with the incidence of ibuprofen and naproxen. The results indicate that the new agent is associated with no statistically or clinically significant reduction in ulceration or bleeding with long-term use compared with ibuprofen and naproxen. The investigators of the study argue that the lack of difference in safety is because the drug is being promoted as safer; therefore, most patients receiving it are at a much higher baseline risk of NSAID-induced ulceration and bleeding. If this phenomenon did indeed affect the study results, which potential source of bias would most likely be present?

A. Recall bias.

B. Misclassification bias.

C. Interviewer bias.

D. Channeling bias.

15. A new enzyme immunoassay for HCV RNA has a reported sensitivity of 95% and a specificity of 92%. If the prevalence of HCV in a cohort of 500 patients is 40%, which value best represents the positive predictive value of this new test?

A. 75%.

B. 89%.

C. 92%.

D. 96%.

BPS Pharmacotherapy Specialty Examination Content

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.1 – 1.1.3, 1.1.6, 1.1.8, 1.1.10 – 1.1.17
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.1 – 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1 – 1.3.7
2. Application of Evidence to Practice and Education
    a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Sub-task(s): 2.1.5
    b. 2.2. Evaluate pharmacotherapy-related literature and health information. Sub-task(s): 2.2.1, 2.2.3, 2.2.12
3. Healthcare Systems and Population Health
    a. 3.3. Incorporate public health initiatives to improve population health. Sub-task(s): 3.3.1 – 3.3.3

I. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

A. Definition:
   1. GERD is defined by consensus as "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung." (Am J Gastroenterology 2013;108:308-28). Strength of guideline evidence is rated by the GRADE system (Level of Evidence and Strength).
   2. Definition subdivides GERD into the following categories:
      a. Symptoms without erosions on endoscopy (nonerosive reflux disease)
      b. Symptoms with erosions on endoscopy (erosive reflux disease)
   3. Symptoms
      a. Typical symptoms: Heartburn (pyrosis), regurgitation, acidic taste in the mouth
      b. Extraesophageal or atypical symptoms: chronic cough, asthma-like symptoms, recurrent sore throat, laryngitis or hoarseness, noncardiac chest pain. Sinusitis, pneumonia, bronchitis, otitis media are less common atypical symptoms. These symptoms require referral for additional testing.
      c. Alarm symptoms: dysphagia, odynophagia, bleeding, weight loss, choking, chest pain, and epigastric mass. These symptoms warrant immediate referral for more invasive testing.
   4. Aggravating factors: recumbency (gravity), elevated intra-abdominal pressure, reduced gastric motility (e.g., gastroparesis), decreased lower esophageal sphincter (LES) tone, and direct mucosal irritation.
   5. Long-term complications: esophageal erosion, strictures, obstruction, Barrett esophagus (replacement of squamous epithelial cells with columnar epithelial cells within the lower esophagus, resulting in increased risk of esophageal carcinoma), and reduction in quality of life.

B. Diagnosis
   1. Symptoms
      a. A presumptive diagnosis of GERD can be made given typical heartburn and regurgitation symptoms. Empiric therapy with a proton pump inhibitor (PPI) is recommended (Strong recommendation/Moderate level of evidence).
      b. Screening for *H. pylori* is not recommended (Strong/Low). *H. pylori* screening is recommended in patients with PUD, a history of a documented peptic ulcer, or gastric mucosa-associated lymphoid tissue (MALT) lymphoma.
      c. Patients with noncardiac chest pain that is suspected to be due to GERD should have a diagnostic evaluation before initiation of therapy (Strong/Low).
   2. Endoscopy: Upper endoscopy is not necessary in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and in the screening of patients at high risk of complications. Repeated endoscopy is not indicated in patients without Barrett esophagus in the absence of new symptoms (Strong/Moderate).
   3. Manometry: Testing to determine esophageal pressure is recommended for preoperative evaluation, but it has no role in the diagnosis of GERD (Strong/Low).
   4. Ambulatory pH testing
      a. Ambulatory esophageal reflux monitoring is indicated before considering endoscopic or surgical therapy in patients with nonerosive reflux disease as part of the evaluation of patients who are refractory to PPI therapy and when the diagnosis of GERD is in question (Strong/Low).
      b. Ambulatory reflux monitoring is the only test that can assess reflux symptom association (Strong/Low).
      c. Ambulatory reflux monitoring is not necessary in the presence of short- or long-segment Barrett esophagus to establish a diagnosis of GERD (Strong/Moderate).

C. Treatment Strategies for GERD
   1. Nonpharmacologic interventions and lifestyle modifications are unlikely to control symptoms in most patients. American College of Gastroenterology (ACG) guidelines cite insufficient evidence to advocate lifestyle modifications for all patients; rather, they advocate use in targeted populations. Thus, the following lifestyle modifications should be implemented only in the patient populations specified.
      a. Dietary modifications to avoid foods that trigger GERD symptoms and to avoid eating meals 2-3 hours before bed (Conditional/Low).
      b. Weight loss if overweight or obese (Moderate/Strong)
      c. Avoid tobacco products or smoking (Conditional/Low)
      d. Elevate head of bed if nocturnal symptoms present (Conditional/Low).
   2. Pharmacologic therapies
      a. Initial treatment depends on the severity, frequency, and duration of symptoms.
         i. "Step-down" treatment: starting with maximal therapy, such as therapeutic doses of PPIs, is always appropriate as a first-line strategy in patients with documented esophageal erosion. Advantages: rapid symptom relief, avoidance of over-investigation. Disadvantages: potential overtreatment, higher cost, increased potential for adverse effects.
         ii. "Step-up" treatment: starting with lower-dose over-the-counter (OTC) products for patients with less severe symptoms without evidence of esophageal erosion. Advantages: avoids overtreatment, has lower initial cost. Disadvantages: potential undertreatment (partial symptom relief; may take longer for symptom control; may lead to over-investigation).
      b. The ACG and American Gastroenterological Association treatment guideline recommendation summary follows in Table 1.

Table 1. American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) Treatment Guideline Recommendation

Area	Recommendation (Level/Strength)
Treatment	Treatment duration of 4-8 weeks (AGA) or 8 weeks (ACG, strong/moderate) of once-daily PPI
	Use maintenance PPIs if return of symptoms or complications (Strong/Moderate)
	Long-term maintenance should be the lowest effective dose, on demand, or intermittent therapy (Conditional/Low)
	Bedtime H_2RAs can be used if morning PPI and nighttime symptoms, but tachyphylaxis develops (Conditional/Low)
	Further testing needed before use of metoclopramide or baclofen (Conditional/Moderate)
Dosing	Traditional PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) should be given 30–60 minutes before meals (Strong/Moderate)
	Newer PPIs (omeprazole-sodium bicarbonate and dexlansoprazole) offer dosing flexibility in relation to meals (Conditional/Moderate)
	Initiate PPIs once daily before a.m. meal (Strong/Moderate)
	Twice-daily PPIs if partial response to once-daily PPIs or nighttime symptoms (Strong/Low)
	Twice daily if partial response to once daily or can switch to another PPI (Conditional/Low)

H_2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.

Strength of recommendations is based on the GRADE system of Strong/Conditional strength of evidence and High/Moderate/Low levels of evidence.

c. Antacids
   i. Calcium-, aluminum-, and magnesium-based products are available OTC in a variety of formulations (capsules, tablets, chewable tablets, and suspensions).
   ii. Neutralizing acid and raising intragastric pH results in decreased activation of pepsinogen and increased LES pressure; rapid onset of action but short duration, necessitating frequent dosing.
   iii. Some products (Gaviscon) also contain the antirefluxant alginic acid, which forms a viscous layer on top of gastric contents to act as a barrier to reflux (variable added efficacy).
   iv. Used as first-line therapy for intermittent (less than twice weekly) symptoms or as breakthrough therapy for those on PPI/histamine-2 receptor antagonist (H_2RA) therapy; not appropriate for healing established esophageal erosions.
   v. Adverse reactions: Constipation (aluminum, calcium), diarrhea (magnesium), accumulation of aluminum and magnesium in renal disease with repeated dosing
   vi. Drug interactions: Chelation (e.g., fluoroquinolones, tetracyclines); reduced absorption because of increases in pH (e.g., ketoconazole, itraconazole, iron, atazanavir, rilpivirine, ledipasvir, velpatasvir, nelfinavir)

d. H_2RAs
   i. Reversibly inhibit histamine-2 receptors on the parietal cell
   ii. All agents available as prescription and/or OTC products; a variety of formulations available; generics exist for all prescription products. See Table 2 for available H_2RA formulations.
   iii. Recent U.S. Food and Drug Administration (FDA) safety alerts have resulted in withdrawal from the market of ranitidine products because of the presence of N-nitrosodimethylamine (NDMA), a carcinogen.

Table 2. Histamine-2 Receptor Antagonists

Agent	Oral OTC Formulations	Oral Prescription Formulations	Usual GERD therapeutic dose
Cimetidine (Tagamet)	200-mg tablet (Tagamet-HB)	200-, 300-, 400-, 800-mg tablets 300 mg/5 mL of solution	400 mg PO QID or 800 mg PO BID
Nizatidine (Axid)	Not available	150-mg/300-mg capsules 15 mg/mL of solution	150 mg PO BID
Famotidine (Pepcid, Zantac) Pepcid Complete	10- and 20-mg tablets 10 mg + 800 mg of calcium carbonate + 165 mg of magnesium hydroxide chewable tablets (Pepcid Complete)	20-mg/40-mg tablets 40-mg/5-mL suspension	20 or 40 mg PO BID

BID = twice daily; OTC = over the counter.

   iv. OTC H_2RAs can be used for on-demand therapy for intermittent mild-to-moderate GERD symptoms; preventive dosing before meals or exercise is also possible. Higher prescription doses are often necessary for more severe symptoms or for maintenance dosing. Prolonged use is associated with the development of tolerance and reduced efficacy (tachyphylaxis).
   v. H_2RAs are less effective than PPIs in healing erosive esophagitis.
   vi. Adverse effects: Most are well tolerated. Central nervous system (CNS) effects such as headache, dizziness, fatigue, somnolence, and confusion are the most common. Older adults and patients with reduced renal function are at higher risk. Prolonged cimetidine use is associated rarely with gynecomastia.

vii. Drug interactions: Can affect the absorption of drugs dependent on lower gastric pH (e.g., ketoconazole, itraconazole, iron, atazanavir) or increases in absorption leading to potential toxicity (e.g., raltegravir). Cimetidine also inhibits cytochrome P450 (CYP) enzymes 1A2, 2C9, 2D6, and 3A4. Warfarin, theophylline, and other agents metabolized by these enzymes can be affected. Cimetidine can also compete with medications and creatinine for tubular secretion in the kidney.

e. Proton pump inhibitors
   i. Irreversibly inhibit the final step in gastric acid secretion; greater degree of acid suppression achieved and typically longer duration of action than H_2RAs
   ii. Most effective agents for short- and long-term management of GERD and for management of erosive disease
   iii. Several PPIs are available as generic prescription-strength products (e.g., omeprazole, lansoprazole, pantoprazole). Omeprazole, lansoprazole, and esomeprazole are available OTC. The OTC products are considered safe and effective for intermittent short-term (2 weeks) use in patients with typical heartburn symptoms. Long-term use of OTC products should be discussed with prescriber to prevent loss of follow-up or to assess for potential over or undertreatment.
   iv. Most effective when taken orally before meals; for divided dosing, give evening dose before evening meal instead of at bedtime. See Table 3 for available PPI products and Table 4 for alternative PPI administration options.

Table 3. Proton Pump Inhibitors

Product	Formulations	Standard dose (High dose)[a]
Dexlansoprazole (Dexilant)	Delayed-release capsule (30 mg/60 mg)	30 mg once daily (60 mg once daily)
Esomeprazole (Nexium) (Nexium 24HR OTC)	Delayed-release capsule IV solution Delayed-release oral suspension Delayed-release capsule Delayed-release capsule or tablet	20 mg once daily (40 mg twice daily)
Esomeprazole strontium	Delayed-release capsule (49.3 mg equivalent to 40 mg esomeprazole)	49.3 mg once daily
Lansoprazole (Prevacid) (Prevacid 24HR)	Prevacid 24HR delayed-release capsule Delayed-release capsule Delayed-release oral suspension Delayed-release orally disintegrating tablet	30 mg once daily (30 mg twice daily)
Omeprazole (Prilosec) Prilosec OTC Zegerid OTC	Delayed-release capsule Delayed-release tablet (magnesium salt) Immediate-release powder for oral suspension; sodium bicarbonate buffer = 460 mg of Na^+/dose (two 20-mg packets are not equivalent to one 40-mg packet) Zegerid OTC immediate-release capsules with sodium bicarbonate	20 mg once daily (40 mg twice daily)

Table 3. Proton Pump Inhibitors *(Cont'd)*

Product	Formulations	Standard dose (High dose)[a]
Pantoprazole (Protonix)	Delayed-release tablet (20 mg/40 mg) IV solution (40 mg/vial) Pantoprazole granules 40 mg/packet	40 mg once daily (40 mg twice daily)
Rabeprazole (AcipHex)	Delayed-release enteric-coated tablet (20 mg) Sprinkle capsule (5 mg, 10 mg)	20 mg once daily (20 mg twice daily)

[a]High-dose therapy is reserved for patients with inadequate response to standard doses.

IV = intravenous; OTC = over the counter.

Table 4. Alternative administration of PPIs

Product	Alternative Administration Technique
Omeprazole (Prilosec) Esomeprazole (Nexium) Zegerid	Open capsules; mix with applesauce or juice Simplified omeprazole suspension; contents dissolved in bicarbonate (NG/OG) Open esomeprazole capsules and mix with 60 mL of water by NG tube, or dissolve oral suspension in 15 mL of water and administer by NG tube; IV bolus, or continuous infusion Zegerid mix packet with 20 mL water in syringe (NG)
Lansoprazole (Prevacid)	Open capsules; mix with applesauce, ENSURE, cottage cheese, pudding, yogurt, or strained pears, or 60 mL of tomato, orange, or apple juice Open capsules + 40 mL of apple juice (NG/OG) Simplified lansoprazole suspension; contents dissolved in bicarbonate (NG/OG) Do not use oral suspension for NG/OG; mix packet with 30 mL of water and swallow Orally disintegrating tablet by oral syringe: Use 4 mL of water for 15 mg tablet or 10 mL of water for 30 mg tablet Orally disintegrating tablet by NG tube (> 8 French): Same preparation as for oral syringe
Rabeprazole (AcipHex)	Do not crush Empty sprinkle capsule contents into liquid or soft food and administer within 15 min of preparation. Sprinkle capsule should not be swallowed whole or contents chewed or crushed
Pantoprazole (Protonix)	Do not crush IV (bolus or continuous infusion) Pantoprazole suspension (compounded with bicarbonate)
Dexlansoprazole (Dexilant)	Open capsules and sprinkle on applesauce

IV = intravenous; NG = nasogastric; OG = orogastric.

iv. Adverse reactions
   (a) Overall, well tolerated; possible adverse effects include headache, dizziness, nausea, diarrhea, and constipation. Long-term use is not associated with significant increases in endocrine neoplasia or symptomatic vitamin B_{12} deficiency. As an option, the 2013 American Gastroenterological Association guidelines list the switching of PPIs in patients having adverse effects (Conditional/Low).
   (b) Summary of major adverse effects of PPIs and prevention and management strategies can be found in Table 5.

Table 5. Summary of Major Adverse Effects of PPIs and Prevention and Management Strategies

Adverse Effect	Prevention and Management
Acute interstitial nephritis (AIN)	Limit the dose and duration of PPIs. Renal function monitoring may not be necessary for short-term use (4–8 weeks) use; consider annual monitoring, dose reduction, and deprescribing in patients with long-term use. AIN may recur with PPI rechallenge
Risk of fracture (hip, wrist, spine)	Concern about fractures should not affect decision to use PPIs, except in patients with other risk factors for hip fracture (Strong/Moderate); patients with osteoporosis can remain on PPIs; limit dose and duration; ensure adequate calcium and vitamin D; BMD screening if at risk of low bone mass; weight-bearing exercise
Hypomagnesemia, iron deficiency, B_{12} deficiency	Reevaluate need of PPI use; limit dose and duration; consider baseline testing if risk factors for deficiciency are present; supplementation
Clostridioides difficile–associated diarrhea	Reevaluate need of PPI use; limit dose and duration; evaluate for *C. difficile* if patient receiving PPI has diarrhea that is not improving; have patients report diarrhea
Community-acquired pneumonia	Short-term use may increase risk; long-term risk is not elevated (Conditional/Moderate); assess vaccine status

BMD = bone mineral density; PPI = proton pump inhibitor.

v. Drug interactions
   (a) Inhibition of CYP450: Omeprazole inhibits the metabolism of substrates, such as diazepam, through CYP2C19 inhibition.
      (1) Potential reduced effectiveness of clopidogrel through inhibition of CYP2C19-mediated conversion to active metabolite by omeprazole. Recommendations from the FDA are to avoid omeprazole and to use pantoprazole as an alternative. The 2013 ACG guidelines consider the PPI/clopidogrel interaction not clinically significant (Strong/High).
      (2) Interaction with high-dose intravenous methotrexate. The labeling for both intravenous methotrexate and the PPIs has been updated to include this interaction, which places patients at higher risk of methotrexate toxicity. Proposed mechanisms include reduced methotrexate excretion by PPI inhibition of BCRP (breast cancer resistance protein), an efflux pump that transports methotrexate across membranes, or reduced renal excretion by inhibition of renal H^+/K^+-ATPase. Patients receiving high-dose intravenous methotrexate should avoid PPI use, with a switch to an H2RA if needed. Holding the PPI dose for 2 days before and after methotrexate administration can prevent the interaction.
   (b) Drugs with pH-dependent absorption (e.g., ketoconazole, itraconazole, atazanavir, rilpivirine, ledipasvir, velpatasvir)

f. Promotility agents
   i. Current guidelines recommend against prokinetic agents for GERD treatment unless there is objective evidence of gastroparesis (Low/Strong).
   ii. Metoclopramide: dopamine antagonist; dosed several times a day; associated with adverse effects such as dizziness, fatigue, drowsiness, extrapyramidal symptoms (EPS), and hyperprolactinemia; 5- and 10-mg ODT formulations are available; used for GERD and diabetic gastroparesis.
   iii. Bethanechol: cholinergic agonist; poorly tolerated because of adverse effects such as diarrhea, blurred vision, and abdominal cramping; may also increase gastric acid production. Used for urinary retention, off-label for GERD

g. Sucralfate is not recommended in the routine treatment of GERD except in the setting of pregnancy (Low/Strong).

h. Surgical therapy
    i. Surgical therapy (Nissen fundoplication) is a laparoscopic procedure for long-term therapy in patients with GERD (Strong/High).
    ii. Surgical therapy is generally not recommended in patients who do not respond to PPI therapy (Strong/High).
    iii. Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon (Strong/High).
    iv. Patients with obesity contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients (Conditional/Moderate).
    v. Current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy (Strong/Moderate).

D. Management of dyspepsia was recently reviewed by ACG and the Canadian Association of Gastroenterology. The recommendations include endoscopy for patients at risk for serious outcomes, testing and eradicating *H. pylori*, and using PPIs, tricyclic antidepressants, prokinetic agents, and psychotherapy to manage symptoms.

Patient Case

1. A 55-year-old man with an 8-month history of GERD symptoms 4–5 days/week has been receiving lansoprazole 15 mg daily by mouth, with the use of magnesium hydroxide for breakthrough symptoms. His symptoms are still present 3–4 days/week and are disruptive to his daily life. He has implemented lifestyle modifications and has been adherent to lansoprazole. His medical history is significant for hypothyroidism. He takes levothyroxine 100 mcg once daily. An endoscopy last week revealed no ulcers or erosions. Which treatment approach is best for this patient?
    A. Add metoclopramide 10 mg four times daily.
    B. Increase lansoprazole to 15 mg twice daily.
    C. Switch to omeprazole 20 mg daily.
    D. Add sucralfate 1000 mg four times daily.

II. PEPTIC ULCER DISEASE

A. Classification of peptic ulcer disease (PUD)
    1. Duodenal ulcer
        a. Common causes: *H. pylori* infection (95%), NSAIDs, low-dose aspirin
        b. Uncommon causes: Zollinger-Ellison syndrome, hypercalcemia, granulomatous diseases, neoplasia, infections (cytomegalovirus, herpes simplex, tuberculosis)
        c. Presentation: epigastric pain, possibly worse at night; often, pain occurs 1–3 hours after a meal and may be relieved by eating. Pain may also be episodic. Associated symptoms can include heartburn, belching, a bloated feeling, nausea, and anorexia.
    2. Gastric ulcer
        a. Common causes: NSAIDs, *H. pylori* infection
        b. Uncommon causes: Crohn disease (CD), infections (cytomegalovirus, herpes simplex)
        c. Presentation: epigastric pain, often made worse by eating; associated symptoms may include heartburn, belching, a bloated feeling, nausea, and anorexia

3. Complications of PUD
   a. Bleeding
   b. Gastric outlet obstruction
   c. Perforation
4. Patients at risk of NSAID-induced GI toxicity: Risk factors for NSAID-induced GI complications can be found in Table 6.

Table 6. Risk Factors for NSAID-Induced Gastrointestinal Complications

Category	Risk Factors
High risk	History of complicated ulcer Several (> 2) risk factors
Moderate risk (1 or 2 risk factors)	Age > 65 yr High-dose NSAID therapy (e.g., ibuprofen 2400 mg/day, naproxen 1000 mg/day) History of uncomplicated ulcer Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants
Low risk	No risk factors

NSAID = nonsteroidal anti-inflammatory drug.

   a. Some NSAIDs such as ibuprofen, diclofenac, and nabumetone are intrinsically less toxic to the GI tract than naproxen, which is considered a moderate risk. Other agents such as piroxicam, indomethacin, and ketorolac are considered high-risk agents.
   b. Duration of NSAID use (higher risk in first 3 months). The presence of chronic debilitating disorders, such as rheumatoid arthritis or cardiovascular (CV) disease, could also contribute to the increased GI toxicity of NSAIDs, but these are not generally considered independent risk factors.
   c. *H. pylori* infection is thought to confer additive risk of GI toxicity in NSAID users; however, evidence of H. pylori eradication in patients using NSAIDs is not conclusive..
5. Diagnosis
   a. Symptom presentation
   b. Testing for *H. pylori* infection: Practitioners must be willing to treat if test results are positive, because *H. pylori* is a known carcinogen.
      i. Testing is indicated for patients with active ulcer disease, history of PUD, or gastric MALT lymphoma.
      ii. The *H. pylori* test-and-treat strategy is also acceptable for patients with unevaluated dyspepsia without alarm symptoms who are younger than 60 years.
   c. Diagnostic tests for *H. pylori* infection
      i. Noninvasive tests are preferred over invasive tests for ease of use.
         (a) Serologic tests (QuickVue *H. pylori* gII, FlexSure HP): Detect immunoglobulin (Ig) G to *H. pylori* in the serum by enzyme-linked immunosorbent assay (85% sensitive, 79% specific). Cannot distinguish between active infection and past exposure. Because antibodies persist for long periods after eradication, cannot use to test for eradication after treatment.
         (b) Urea breath test (UBT; BreathTek UBT, PYtest) detects the exhalation of radiolabeled CO_2 after the ingestion of ^{13}C- or ^{14}C-radiolabeled urea. *H. pylori* hydrolysis of the radiolabeled urea results in CO_2 production (97% sensitive, 95% specific. It is used to make a diagnosis and to test for eradication. Recent use of antibiotics or PPIs can cause false-negative results in up to 40% of patients. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before UBT testing or wait 4 weeks after treatment has ended before having the UBT performed.

(c) Stool antigen tests (Premier Platinum HpSA, ImmunoCard STAT! HpSA) are polyclonal or monoclonal antibody tests that detect the presence of *H. pylori* in stool (88%–92% sensitive, 87% specific). They can be used to make a diagnosis and to confirm eradication. Recent use of bismuth, antibiotics, or PPIs can also cause false-negative results. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before stool antigen testing or wait 4 weeks after treatment has ended before having the stool antigen test performed.

ii. Invasive (endoscopic) tests are used less frequently than noninvasive tests.
   (a) Histology: 90%–95% sensitive, 98%–99% specific, subject to sampling error
   (b) Rapid urease tests (*Campylobacter*-like organism [CLO] test, Hp-fast, and PyloriTek) detect the presence of ammonia (NH_3) in a sample generated by *H. pylori* urease activity (80%–95% sensitive, 95%–100% specific). False-negative results can be caused by a partly treated infection, GI bleeding, achlorhydria, or use of PPIs, H_2RAs, or bismuth. Patients should discontinue antisecretory agents for at least 1 week before the test is performed.
   (c) Culture is costly, time-consuming, and technically difficult (100% specific).

B. Treatment of *H. pylori*–associated ulcers
   1. General recommendations, based on ACG guidelines, are to include an antisecretory agent (preferably a PPI) plus at least two antibiotics (clarithromycin and amoxicillin or metronidazole) in the eradication regimen. Specific treatment regimens are listed in Table 7.
   2. Quadruple therapy with bismuth subsalicylate, metronidazole, tetracycline (or doxycycline in the case of drug shortages), and a PPI is considered an alternative first-line treatment. Pylera, a quadruple based therapy formulated with tetracycline, bismuth subcitrate, and metronidazole in 1 capsule, can be used by patients with aspirin allergy.
   3. Sequential therapy involves administration of a PPI and amoxicillin given for the first 5 days, followed by a PPI, clarithromycin, and tinidazole for an additional 5 days. This therapy requires further validation before widespread use will be accepted.
   4. A bismuth-based quadruple therapy for 14 days or a levofloxacin-based triple therapy for 10 days can be used in patients who have not responded to initial regimens as salvage therapy.
   5. Follow-up testing for eradication should be performed in patients with a history of ulcer complication, MALT lymphoma, early gastric cancer, or recurrence of symptoms.
   6. UBTs or stool antigen tests are preferred for confirming eradication (should wait at least 4 weeks after treatment for both).
   7. Patients should be asked about prior use of antibiotics, and this information should be considered when the treatment regimen is chosen (ACG).

Table 7. Recommended Treatment Regimens for *Helicobacter pylori* Infection

Regimen	Drugs and doses	Notes
Clarithromycin triple	PPI (standard or double dose) BID + amoxicillin 1000 mg BID or metronidazole 500 mg TID + clarithromycin 500 mg BID for 14 days	Avoid if clarithromycin resistance rate is known to be > 15% or in patients with prior macrolide exposure
Bismuth quadruple	PPI (standard dose) BID + Bismuth subsalicylate 300 mg QID or Bismuth subcitrate 120-300 mg QID + metronidazole 250 QID or 500 mg TID-QID + tetracycline 500 mg QID x 10-14 days	Initial treatment choice if clarithromycin resistance rates are high or patient has prior macrolide exposure. Also beneficial to patients with penicillin allergy

Table 7. Recommended Treatment Regimens for *Helicobacter pylori* Infection *(continued)*

Regimen	Drugs and doses	Notes
Concomitant	PPI (standard dose) BID + clarithromycin 500 mg BID + amoxicillin 1000 mg BID + metronidazole or tinidazole 500 mg BID for 10-14 days	Appears at least as effective as clarithromycin triple therapy, although not validated in North America
Sequential	PPI (standard dose) BID + amoxicillin 1000 mg BID for 5–7 days; then PPI BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 5–7 days	Efficacy subject to geographic variation of resistance rates; complexity of regimen makes it less desirable as first line therapy
Hybrid	PPI (standard dose) BID + amoxicillin 1000 mg BID for 7 days; then PPI BID + amoxicillin 1 g BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 7 days	Regimen not studied in North America; complexity of regimen makes it less desirable as first line therapy
Levofloxacin triple	PPI (standard dose) BID + levofloxacin 500 mg daily + amoxicillin 1000 mg BID for 10–14 days	Lack of North American data; concerns for high levofloxacin resistance rates. Additional risks associated with fluoroquinolone therapy such as high North American resistance rates and adverse affects should be considered
Levofloxacin sequential	PPI (standard or double dose) BID + amoxicillin 1000 mg BID for 5-7 days; then PPI BID + amoxicillin 1000 mg BID + levofloxacin 500 mg daily + metronidazole or tinidazole 500 mg BID for 5-7 days	Lack of North American data; may be more effective than levofloxacin triple therapy
LOAD	PPI (double dose) daily + levofloxacin 250 mg daily + metronidazole or tinidazole 500 mg BID + doxycycline 100 mg daily	Lack of North American data; may be more effective than levofloxacin triple therapy

BID = twice daily; PPI = proton pump inhibitor; QID = four times daily; TID = three times daily.

C. Primary prevention of NSAID-induced ulcers
   1. Implement risk factor modification.
   2. Test and treat for *H. pylori* infection if the patient is beginning long-term NSAID therapy.
   3. Determine the level of GI-related risk (low, medium, high) using Table 6. See Box 1 for strategies to prevent GI complications in patients receiving NSAIDs based on their CV risk.
   4. Because of the association of increased risk of CV events with NSAID use, the patient's CV risk should be determined as well. The ACG guidelines define those at high CV risk as patients who require low-dose aspirin for the prevention of cardiac events. Naproxen is the only NSAID that does not appear to increase the risk of CV events; therefore, its use is preferred in patients with CV risk factors per the ACG guidelines. However, in 2015, the FDA required that warnings regarding the risk of myocardial infarction and strokes be attached to NSAID products (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory).

Box 1. Preventive Strategies Based on Risk of NSAID-Related GI Complications and CV Risk

If low CV risk and:
Low GI risk[a] → NSAID (lowest dose of least ulcerogenic agent)
Moderate GI risk[b] → NSAID + PPI or misoprostol
High GI risk[c] → COX-2 inhibitor + PPI or misoprostol
If high CV risk (requirement for low-dose aspirin) and:
Low GI risk[a] → Naproxen + PPI or misoprostol
Moderate GI risk[b] → Naproxen + PPI or misoprostol
High GI risk[c] → Avoid NSAIDs or COX-2 inhibitors

[a]No risk factors.

[b]One or two risk factors present (see Table 6).

[c]Positive history of ulcer complication or several (more than two) risk factors or use of steroids and anticoagulants.

COX-2 = cyclooxygenase-2; CV = cardiovascular; NSAID = nonsteroidal anti-inflammatory drug.

5. Misoprostol (Cytotec) should be given at full doses (800 mcg/day in four divided doses); however, this therapy is poorly tolerated because of excessive nausea, vomiting, diarrhea, and abdominal cramping.
6. Concomitant use of antiplatelet agents and NSAIDs
    a. Need for antiplatelet therapy should first be evaluated.
    b. If antiplatelet therapy is deemed necessary, assess for the presence of GI risk factors (see Table 6). Dyspepsia or GERD symptoms are additional risk factors.
    c. Test and treat for *H. pylori* in patients with a history of a nonbleeding ulcer and in those with a history of an ulcer-related complication. Eradicating *H. pylori* before beginning long-term antiplatelet therapy is optimal.
    d. PPIs are the preferred gastroprotective agents for both treatment and prevention of aspirin- and NSAID-associated GI injury.
    e. Gastroprotective therapy should be prescribed for patients with GI risk factors who require the use of any NSAID (including OTC and cyclooxygenase-2 [COX-2] inhibitors) in conjunction with low-dose aspirin.
    f. Gastroprotective therapy should be prescribed for patients with GI risk factors who require low-dose aspirin. Aspirin doses greater than 81 mg/day should not be used in patients with GI risk factors during the long-term phase of aspirin therapy.
    g. PPIs should be prescribed for patients receiving concomitant aspirin and anticoagulant therapy (unfractionated heparin, low-molecular-weight heparin, argatroban, warfarin, direct oral anticoagulants, and fondaparinux).
    h. The target INR range of 2–2.5 should be used in patients for whom warfarin is added to concomitant aspirin and $P2Y_{12}$ inhibitor (e.g., clopidogrel, prasugrel, ticagrelor) therapy. The combination of both aspirin and clopidogrel with warfarin should be used only when benefit outweighs risk.
    i. Clopidogrel is not recommended as a substitute for patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel for GI bleed risk.
    j. The health care provider (HCP) who decides to discontinue aspirin therapy in patients with short-term bleeding episodes should weigh the risks of subsequent GI or cardiac events.
    k. For patients receiving dual antiplatelet therapy (aspirin plus clopidogrel) who require elective endoscopy (particularly colonoscopy and polypectomy), consider deferring if patient is at high risk of cardiac events. Elective endoscopy should be deferred for 1 year after the placement of drug-eluting stents.

D. Treatment and secondary prevention of NSAID-induced ulcers
   1. Risk factor modification
   2. Discontinue or lower NSAID dose, if possible. Ulcers will heal with appropriate treatment, but healing may take longer with continued NSAID use.
   3. Test for *H. pylori* and treat, if present.
   4. Drug therapy
      a. PPIs: Drugs of choice for healing and secondary prevention of NSAID-induced ulcers. Combination product Vimovo contains esomeprazole with naproxen in the same tablet (375 mg/20 mg or 500 mg/20 mg) but may be expensive.
      b. Misoprostol appears to be as effective as PPIs for healing and secondary prevention; however, it necessitates several doses per day, and it is poorly tolerated because of the high incidence of diarrhea and abdominal pain.
      c. COX-2 inhibitors: Celecoxib was shown to have rates of ulcer recurrence and bleeding comparable to those of a diclofenac plus omeprazole combination. The use of celecoxib may be limited by its association with CV effects. The use of celecoxib is also uncertain in combination with low-dose aspirin for secondary prevention of GI events.
      d. The combination of a COX-2 inhibitor and a PPI is not well studied, but it can be considered in high-risk patients, especially if receiving aspirin plus steroids or warfarin or have a history of a recent complicated GI event and require continued NSAID or aspirin use.
      e. H_2RAs are inferior to misoprostol and PPIs in healing and preventing recurrence.
      f. Clopidogrel is not recommended as a substitute in patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel for GI bleed risk.
   5. CV safety of COX-2 inhibitors and NSAIDs
      a. The main theory underlying the development of excess thrombotic events with COX-2 inhibitor use is that when COX-2–mediated prostacyclin production is reduced, the prothrombic prostaglandin thromboxane A continues to be produced by COX-1, leading to the development of a prothrombic state.
      b. Celecoxib was not associated with increases in CV events until the Adenoma Prevention with Celecoxib trial for cancer prevention was terminated in 2004. Daily doses of 400 and 800 mg of celecoxib conferred a 2.5- and 3.4-fold higher risk of fatal and nonfatal myocardial infarction respectively, which suggests a dose-related response for this toxicity.
      c. The AHA recommends a stepped approach for patients with CV disease or risk factors for ischemic heart disease who require analgesic treatment of musculoskeletal symptoms.
         i. Consider using acetaminophen, aspirin, tramadol, or short-term narcotics first.
         ii. Nonacetylated salicylates (e.g., salsalate, choline magnesium trisalicylate) can be considered next.
         iii. Non–COX-2-selective NSAIDs can be used next, followed by NSAIDs with some COX-2 activity. Use the lowest possible effective dose.
         iv. Celecoxib should be reserved as a last resort. In patients at increased risk of thromboembolic events, coadministration with aspirin and a PPI can be considered.
         v. Routinely monitor blood pressure, renal function, and signs of edema or GI bleeding.
      d. Methods to reduce CV risk, such as tobacco cessation, blood pressure reductions, lipid control, and glucose control, are recommended for NSAID users, but have not been proved to reduce NSAID-associated CV risk. In patients for whom the risk of GI bleeding outweighs the CV risk, lower-risk NSAIDs such as ibuprofen, etodolac, diclofenac, or celecoxib should be used. In patients for whom the CV risk outweighs the risk of GI bleeding, COX-2 inhibitors should be avoided. Limit the dose and therapy duration, if possible.

e. The AHA recommends that ibuprofen be taken at least 30 minutes after or 8 hours before the ingestion of immediate-release low-dose aspirin to prevent the ibuprofen from attenuating the antiplatelet effects of the aspirin.

Patient Cases

2. A 68-year-old woman referred to a gastroenterologist has intermittent upper abdominal pain with anemia and heme-positive stools. She has a history of hypertension and type 2 diabetes with peripheral neuropathy. She reports no known drug allergies and takes metformin 1000 mg twice daily, aspirin 325 mg daily, lisinopril 20 mg daily, and gabapentin 1000 mg three times daily. In addition, she reports using OTC ketoprofen daily for the past 2 months secondary to uncontrolled pain. The results of a colonoscopy are negative, but endoscopy reveals a 1-cm gastric ulcer with an intact clot. A rapid urease test for CLO is negative. Which treatment is best for this patient's ulcer?
   A. Cimetidine 800 mg twice daily for 4 weeks.
   B. Lansoprazole 30 mg twice daily plus amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily for 10 days.
   C. Lansoprazole 30 mg/day for 8 weeks.
   D. Misoprostol 200 mcg twice daily for 8 weeks.

3. A 42-year-old man is in the clinic with the chief concern of sharp epigastric pain for the past 6 weeks. He states that the pain is often worse with eating and that it is present at least 5 days/week. He states that although he initially tried OTC antacids with some relief, the pain returns about 3 hours after each dose. He currently takes no other medications. He reports an allergy to sulfa-containing medications (rash). His practitioner is concerned about a potential peptic ulcer and tests him for *H. pylori* using a UBT, the result of which is positive. Which treatment for *H. pylori* is best?
   A. Amoxicillin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 5 days.
   B. Cephalexin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 10 days.
   C. Bismuth subsalicylate 525 mg four times daily plus tetracycline 500 mg four times daily plus metronidazole 500 mg three times daily plus omeprazole 20 mg twice daily for 14 days.
   D. Levofloxacin 500 mg once daily plus metronidazole 500 mg twice daily plus omeprazole 20 mg twice daily for 21 days.

III. UPPER GI BLEEDING

A. Causes of upper GI bleeding
   1. Peptic ulcer disease (40%–70%) due to NSAIDs and low-dose aspirin use or *H. pylori*
   2. Esophagitis
   3. Erosive disease
   4. Esophageal varices
   5. Mallory-Weiss tear (longitudinal mucosal lacerations in the lower esophagus or upper stomach)
   6. Neoplasm
   7. Stress ulcers (critically ill patients)

B. Clinical Symptoms and Presentation
   1. Hematemesis or "coffee-ground" emesis
   2. Hematochezia
   3. Nausea, vomiting
   4. Melena
   5. Shock (tachycardia, clammy skin)
   6. Hypotension
   7. Associated organ dysfunction (renal, hepatic, cardiac, cerebral hypoperfusion)

Box 2. Clinical Predictors of Death Associated with Nonvariceal Upper GI Bleeding

Advanced age (> 75 yr at highest risk)	Elevated serum urea
Blood in gastric aspirate	Red blood on rectal examination
Continued bleeding or rebleeding	SCr > 150 μmol/L (1.7 mg/dL)
> 1 comorbid condition	Sepsis
Elevated aminotransferases	Shock or hypotension

Box 3. Predictors of Persistent or Recurrent Upper GI Bleeding

Age > 65 yr	Gastric or duodenal ulcer
Blood in gastric aspirate	Hematemesis
Coagulopathy	Initial hemoglobin < 10 g/dL or hematocrit < 30%
Comorbid illness	Location of ulcer on superior or posterior wall
Endoscopic findings:	Melena
Active bleeding on endoscopy	Ongoing bleeding
Presence of high-risk stigmata	Red blood on rectal examination
Adherent clot	Shock (systolic blood pressure < 100 mm Hg)
Erratic mental status	Ulcer size ≥ 2 cm

C. Management of ulcer-related GI bleeding
   1. Volume resuscitation and hemodynamic stabilization
      a. Placement of one or two large-bore intravenous catheters
      b. Replacement with crystalloid such as 0.9% normal saline is preferred; colloids such as blood can be given after initial resuscitation in patients with hemoglobin of less than 7 g/dL to maintain a hemoglobin concentration of 8–10 g/dL.
   2. Risk stratification
      a. Clinical signs and symptoms
      b. Use of clinical scoring scales such as Glasgow-Blatchford scores to determine the risk of early rebleeding and the need for urgent versus nonemergency intervention. Patients with very low risk of rebleeding (Glasgow-Blatchford score of 0–1) can be discharged for outpatient follow-up (conditional recommendation, very-low-quality evidence).
      c. Placing an NG tube for aspiration can be considered but is not required.
      d. Endoscopy (within 24 hours if possible, 12 hours with high-risk clinical features)
      e. Assessment of comorbid illnesses (liver disease, coagulopathies, cardiac status)
      f. Predictive factors of death with upper GI bleed are listed in Box 2. Predictors of persistent or recurrent GI bleeding are listed in Box 3.

3. Endoscopic therapy
    a. Endoscopic therapy is associated with reductions in rebleeding, need for surgery, and mortality. Perform within 24 hours of presentation.
    b. The combination of injection and coaptive therapy is the most efficacious; the use of either technique plus pharmacotherapy is superior to monotherapy.
4. Pharmacotherapeutic management of nonvariceal upper GI bleeding
    a. Remove medications that are contributing to bleeding (e.g., NSAIDs).
    b. PPI therapy
        i. Use of a pre-endoscopic dose (80-mg intravenous bolus, followed by an 8-mg/hour intravenous infusion) of PPI may be considered. This does not result in reduced mortality, surgery, or rate of rebleeding, but it can reduce the lesion size, the possibility of finding a high-risk lesion, and the need for endoscopic therapy. PPIs may be given if endoscopy will be delayed or cannot be performed.
        ii. Continuous or intermittent proton pump inhibitor antisecretory therapy is recommended (Am J Gastroenterol 2021;116:899-917).
            (a) Bolus 80 mg plus a continuous infusion of 8 mg/hour for 72 hours after endoscopic therapy for patients with active bleeding or nonbleeding visible vessel or with adherent clot. Intravenous pantoprazole or esomeprazole can be used; most data are with intravenous omeprazole (used in Europe).
            (b) Intermittent intravenous or oral PPI therapy (80-mg intravenous bolus followed by 40 mg two to four times daily for 3 days) is safe and effective.
        iii. Associated with decreases in rebleeding, mortality, and need for surgery in patients with active bleeding who have undergone successful endoscopic intervention.
        iv. Patients who received endoscopic hemostatic therapy and short-term, high-dose PPI should receive twice-daily PPI therapy for 2 weeks (conditional recommendation, low-quality evidence).
        v. Oral once-daily PPI therapy can be used for patients with a flat spot or clean-based ulcer.
    c. The use of H_2RAs or somatostatin-octreotide is not recommended.
    d. Test for *H. pylori* and treat if results are positive. If result are negative, then retest. There is no need for a PPI after eradication.
    e. Assess the need for continued secondary prevention with PPI therapy. If needed, a single daily oral dose of a PPI is recommended.
    f. Assess the need for NSAID or aspirin use. If NSAID therapy is needed, then use of a COX-2 inhibitor plus a PPI is recommended, barring any significant CV risk. Otherwise, a PPI should be used.
    g. If the use of low-dose aspirin is required, reinitiate when CV risk is thought to outweigh GI risk. Use a PPI and reinitiate aspirin within 1–3 days, if not within 1 week. Clopidogrel has a higher rate of rebleeding than aspirin.
    h. Long-term PPI therapy is recommended for ulcers not associated with NSAIDs or *H. pylori*.

D. Prophylaxis of SRMD in critically ill patients
1. Stress-related injury: Superficial diffuse upper GI ulceration
2. Stress ulcer: Deeper mucosal ulceration; may lead to bleeding and hemodynamic compromise
3. Contributing factors to SRMD development
    a. Hypoperfusion of the GI tract
    b. Altered susceptibility to gastric acid
    c. Loss of defense mechanisms: mucous/bicarbonate layer, prostaglandins, cellular renewal
    d. Alterations in gastric motility; may affect absorption of drugs
4. Pharmacologic prevention
    a. Not routinely recommended in non–intensive care unit settings

b. Recommended in patients in an intensive care unit with the risk factors in Box 4.

Box 4. Risk Factors for Initiation of Prophylaxis for SRMD in Intensive Care Units

Mechanical ventilation > 48 hr[a]	Two or more of the following:
Coagulopathy (platelet count < 50,000/mm^3, INR > 1.5)[a]	Sepsis syndrome
Thermal injury (> 35% BSA)	ICU stay > 1 wk
Severe head or spinal cord injury	Occult bleeding
GI bleeding or ulceration within past year	High-dose corticosteroids
Multiple trauma (injury severity score > 16)	(250 mg of hydrocortisone equivalent)
Perioperative transplant period	Hepatic failure
Low intragastric pH	Acute renal insufficiency
Major surgery (lasting > 4 hr)	Hypotension
Acute lung injury	Anticoagulation

[a]Independent risk factors for SRMD.

BSA = body surface area; ICU = intensive care unit; INR = international normalized ratio; SRMD = stress-related mucosal disease.

5. Preventive treatment options
   a. Proton pump inhibitors
      i. The American Society of Health-System Pharmacists guidelines include minimal recommendations for PPI use because of the lack of data at that time; however, PPIs are commonly used for SRMD prevention.
      ii. PPIs are similar to H_2RAs in safety and efficacy.
      iii. Oral or intravenous routes may be used and are equally effective for maintaining gastric pH. Alternative formulations exist for patients with difficulty swallowing or with feeding tubes (see section on GERD).
      iv. In a recent trial, 3298 patients with unplanned intensive care unit admission were randomized to receive either pantoprazole 40 mg intravenously daily or placebo. Mortality at 90 days (primary end point; RR 1.02; 95% CI, 0.91–1.13) and composite event rate, including clinically important GI bleeding, pneumonia, Clostridioides difficile infection, or myocardial infarction (RR 0.96; 95% CI, 0.83–1.11), were similar between groups. Clinically important GI bleeding occurred in 2.5% of patients receiving pantoprazole compared with 4.2% of patients receiving placebo (RR 0.58; 95% CI, 0.4–0.86) (N Engl J Med 2018;379:2199-208).
   b. H_2RAs
      i. Reduce gastric acid secretion by inhibition of histamine stimulation of the parietal cell; development of tolerance or tachyphylaxis with continued use.
      ii. Considered efficacious in the prevention of clinically significant bleeding; oral, intravenous intermittent dosing, and continuous infusion are all possible options. High-dose intravenous (cimetidine or famotidine) use can be considered first-line therapy. Cimetidine is the only H_2RA that is FDA approved for SRMD prevention.
      iii. Associated with CNS adverse effects and the rare development of thrombocytopenia; require adjustment for renal dysfunction
   c. Antacids require several oral doses per day or administration by enteral tube. Diarrhea, constipation, and electrolyte abnormalities are possible.
   d. Sucralfate
      i. Provides a direct mucosal barrier; modulates pepsin, mucus activity, bicarbonate secretion, and tissue growth repair
      ii. Requires many oral doses or administration by enteral tube. May lead to aluminum accumulation and constipation. Possibility of binding to other drugs in GI tract. No effect on platelet count and associated with lower rates of pneumonia development.

IV. INFLAMMATORY BOWEL DISEASE

A. Background
   1. Inflammatory bowel disease (IBD) includes both UC and CD. In some instances, UC may be indistinguishable from CD, called *indeterminate* or *intermediate colitis*.
   2. Pathophysiology: The exact cause of continuing inflammation of the GI mucosa is unknown, but it is thought that the inflammation is secondary to an antigen-driven response.
   3. Contributing factors
      a. Defects in the intestinal epithelial barrier and immune system
      b. There is a definite genetic association; first-degree relatives of affected patients have a 4–20-fold greater risk of developing IBD.
      c. Environmental
         i. NSAIDs: Worsen IBD, probably secondary to alteration of epithelial barrier
         ii. Smoking: Worsens CD; associated with improvement in UC symptoms
         iii. Luminal bacteria: Endogenous intestinal bacteria thought to be highly involved in stimulating the intestinal inflammatory response observed in IBD
         iv. Dietary antigens may also contribute to ongoing inflammation.
      d. Various proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor (TNF), contribute to the ongoing inflammatory process.

B. Clinical features
   1. Presenting symptoms common to UC and CD include fever, abdominal pain, diarrhea (may be bloody, watery, or mucopurulent), rectal bleeding, and weight loss. Symptoms can vary depending on disease location. See Table 8 for the clinical features of IBD.

Table 8. Clinical Features of Inflammatory Bowel Disease

Clinical Findings	Ulcerative Colitis	Crohn Disease
Bowel involvement	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) in a minority of patients	May be anywhere from mouth to anus (66% of cases located in ileum)
Perianal involvement	Unlikely	Yes
Depth of ulceration	Superficial	May extend to submucosa or deeper
Continuous inflammation	Very common	Rarely, a patchy, "cobblestone" appearance
Histology	Nontransmural, crypt abscesses	Transmural lesions, granulomas
Fistula, perforation, or strictures	Very uncommon	Yes
Development of toxic megacolon	Yes	No
Malabsorption or malnutrition	Rare	Yes, often vitamin deficiencies; possible growth retardation in children
Risk factor for colorectal cancer	Yes	Uncommon unless disease affects colon
Pseudopolyps	Common	Fairly uncommon

2. Systemic manifestations
    a. Both UC and CD can present with concurrent systemic manifestations.
    b. Hepatobiliary: primary sclerosing cholangitis, cholangiocarcinoma, hepatitis, cirrhosis, cholelithiasis, steatosis
    c. Rheumatologic arthritis, sacroiliitis, ankylosing spondylitis
    d. Dermatologic: erythema nodosum, aphthous ulcers, pyoderma gangrenosum
    e. Ocular: iritis or uveitis, episcleritis
3. Gauging clinical severity
    a. Ulcerative colitis severity can be determined using Table 9 (based on Truelove and Witt criteria)

Table 9. Clinical Severity of Ulcerative Colitis

Mild	Moderate	Severe	Fulminant
≤4 stools/day (±blood) No fever, anemia, or tachycardia Normal ESR	> 4 stools/day (±blood) Minimal signs of systemic toxicity	> 6 stools/day with blood Body temperature > 99.5°F HR > 90 beats/min ESR > 30 mm/hr Hgb < 75% of normal Abdominal tenderness Bowel wall edema	> 10 stools/day with continuous blood Body temperature > 99.5°F HR > 90 beats/min ESR > 30 mm/hr Transfusions required Abdominal pain Dilated colon

ESR = erythrocyte sedimentation rate; Hgb = hemoglobin; HR = heart rate.

    b. Crohn disease
        i. Mild-moderate: tolerates oral administration; absence of fever, dehydration, and abdominal tenderness; less than 10% weight loss
        ii. Moderate-severe: failed treatment of mild-moderate; anemia, nausea and vomiting, or considerable weight loss usually present
        iii. Severe: no response to outpatient steroids; high temperature, abdominal pain, persistent vomiting; possible obstruction, abscess, cachexia, rebound tenderness
4. General management considerations
    a. Rule out possible infectious causes of bloody diarrhea, especially *C. difficile*, in patients with acute symptoms.
    b. Elevated concentrations of fecal lactoferrin and fecal calprotectin indicate inflammation and help differentiate patients with IBD from those with IBS. These concentrations may also be used to monitor disease activity and therapy response.
    c. Most patients will undergo colonoscopy to confirm the diagnosis and extent of disease. Computed tomography enterography or magnetic resonance enterography can be considered to evaluate inflammation within the ileum in CD.
    d. Surgery is a viable option when complications (abscess, fistula, perforation) occur or when fulminant disease is unresponsive to medical treatment.
    e. Distribution and severity of disease will dictate the initial treatment choice.
    f. Treatment is generally initiated with induction therapy. These treatments are used to acutely control symptoms and inflammation. Once symptoms are controlled, longer-term maintenance therapy is used to control symptoms and inflammation, together with systemic complications. Most patients will require maintenance therapy because of the high incidence of relapse after induction therapy; the relapse rate is 35%–80% at 2 years for CD and 50%–70% at 1 year for UC.

C. Medical management of IBD: adjunctive therapies
   1. Caution in active disease; reduction in motility may precipitate toxic megacolon
   2. Loperamide (Imodium) can be useful for proctitis or diarrhea; 2 mg after each loose stool (16 mg/day maximum)
   3. Antispasmodics (recommended for short-term use)
      a. Dicyclomine (Bentyl), 10–40 mg orally four times daily
      b. Propantheline (Pro-Banthine), 7.5–15 mg orally three times daily
      c. Hyoscyamine (Levsin), 0.125–0.25 mg orally/slow release every 4 hours as needed
   4. Cholestyramine (Questran): for bile salt–induced diarrhea after ileal resection

D. Medications used to treat IBD
   1. Selection of treatment is based on disease location and severity.
   2. Aminosalicylates
      a. Used for both induction and maintenance of remission
      b. Sulfasalazine: prototype agent (Azulfidine, Azulfidine-EN)
         i. Sulfasalazine is cleaved by colonic bacteria to the active portion (5-aminosalicylate) and the inactive carrier molecule sulfapyridine.
         ii. Efficacy is best in colonic disease because of colonic activation of the drug.
         iii. Dose-related adverse effects (due to the sulfapyridine portion): GI disturbance, headache, arthralgia, folate malabsorption
         iv. Idiosyncratic adverse effects: rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis, decreased sperm production in men
         v. Avoid in patients with a sulfa allergy.
         vi. Dosed 2–2.4 g/day orally; available as immediate-release and enteric-coated products. Doses should be titrated beginning at 500–1000 mg once or twice daily to avoid adverse effects.
      c. 5-Aminosalicylates (non–sulfa containing)
         i. Generally better tolerated than sulfasalazine; first line in mild-moderate UC and CD
         ii. Product selection depends on location of disease. Available formulations are listed in Table 10
         iii. Olsalazine is associated with secretory diarrhea in up to 25% of patients.
         iv. Rare instances of nephrotoxicity with use of 5-aminosalicylates

Table 10. Aminosalicylate Formulations

Drug	Trade Names	Formulation	Strength	Daily Dose Range (g)	Site of Action
Mesalamine	Rowasa[a]	Enema	4 g/60 mL	4	Rectum, terminal colon
	Delzicol Asacol HD, Zaldyon	Delayed-release capsule Delayed-release tablet	400 mg 800 mg	1.6–4.8	Distal ileum, colon
	Canasa	Suppository	1000 mg	1	Rectum
	Pentasa	Controlled-release capsule	250 mg 500 mg	2–4	Small bowel, colon
	Lialda	Multimatrix (MMX) delayed-release tablet	1.2 g	2.4–4.8 (once daily)	Colon
	Apriso	Intellicor delayed- and extended-release capsule	0.375 g	0.375–1.5 (once daily)	Colon
Olsalazine	Dipentum	Dimer of mesalamine (capsule)	250 mg	1–3	Colon
Balsalazide	Colazal	Capsule	750 mg	2–6.75	Colon

[a]Generic mesalamine enema available.

3. Corticosteroids
    a. Work quickly to suppress inflammation during acute flares
    b. They have no role in maintenance therapy; however, more than 50% of patients with severe disease may become steroid-dependent.
    c. Budesonide is about 15-fold more potent than prednisone; because of its high first-pass metabolism and limited systemic exposure, allow a 2-week overlap when changing from prednisone to budesonide to prevent adrenal insufficiency. It is formulated to release in the terminal ileum and treats only terminal ileal and ascending colonic disease.
    d. Adverse effects (systemic therapy): adrenal suppression, glucose intolerance, hypertension, sodium/water retention, osteoporosis, cataracts, and impaired wound healing. Systemic adverse effects are minimal with budesonide use.
    e. Available corticosteroid formulation are listed in Table 11

Table 11. Corticosteroid Preparations

Route	Agents	Dose	Comments
Oral	Prednisone Prednisolone	20–60 mg/day	Taper as soon as possible
	Budesonide capsule (Entocort EC 3 mg) Budesonide tablet (Uceris 9 mg)	9 mg/day PO; then 6 mg/day Can be continued for up to 3 mo 9 mg/day in the morning for 8 wk	Minimal absorption, minimal systemic adverse effects; indicated for treatment and maintenance of mild-moderate active CD involving terminal ileum or ascending colon
Intravenous	Hydrocortisone Methylprednisolone	100 mg every 8 hr 15–48 mg/day	7- to 10-day course; change to PO when gut is functional
Topical (rectal)	Cortenema (100 mg/60 mL) Cortifoam (90 mg/applicator) Anucort-HC 25 mg Proctocort 30 mg	100 mg HS 90 mg/day BID 25–50 mg PR BID	Hydrocortisone-based products Used for patients with distal disease Suppositories; use for proctitis
	Uceris rectal foam	2 mg BID x 2 wk; then daily x 4 wk	For induction of remission of mild to moderate distal UC

BID = twice daily; CD = Crohn disease; HS = at bedtime; PO = by mouth; PR = rectally; UC = ulcerative colitis.

4. Immunomodulators
    a. Mercaptopurine (Purinethol), azathioprine (Imuran, Azasan; prodrug of mercaptopurine), methotrexate
    b. Doses: Azathioprine 2–2.5 mg/kg/day orally, mercaptopurine 1–1.5 mg/kg/day orally, methotrexate 15–25 mg/week intramuscularly (CD only)
    c. Indicated only for maintenance because of long onset of action (3–15 months).
    d. Use can result in a steroid-sparing effect.
    e. Azathioprine and mercaptopurine are metabolized by the enzyme thiopurine methyltransferase (TPMT); reduced expression of TPMT can result in slower metabolism and increased toxicity. The TPMT activity or TPMT genotype or phenotype should be determined before initiating therapy.

f. Adverse reactions
    i. Azathioprine and mercaptopurine: pancreatitis (3%–15%), bone marrow suppression, nausea, diarrhea, rash, possible hepatotoxicity. Risk of hepatosplenic T-cell lymphoma, especially in younger male patients or if combined with a TNFα antagonist.
    ii. Methotrexate: bone marrow suppression, nausea, diarrhea, rash, pulmonary toxicity, hepatotoxicity, folate deficiency

5. Small molecules: Oral Janus kinase (JAK) inhibitors indicated for moderate to severe UC after one or more TNF antagonist failure or intolerance.
    a. Tofacitinib (Xeljanz) dosing and outcomes
        i. Induction dosing: 10 mg orally twice daily for at least 8 weeks
        ii. Maintenance dosing: 5–10 mg orally twice daily depending on response
        iii. Discontinue if response is inadequate after 16 weeks of treatment with 10 mg twice daily.
        iv. Dose adjustments
            (a) If receiving a strong CYP 3A4 inhibitor or moderate CYP 3A4 inhibitor and a strong CYP 2C19 inhibitor, or if moderate to severe renal impairment or moderate hepatic impairment: Reduce 10 mg twice daily dose to 5 mg twice daily; reduce 5-mg twice-daily dose to 5 mg once daily.
            (b) If lymphocyte count or absolute neutrophil count is less than 500 cells/mm^3, discontinue tofacitinib.
            (c) If absolute neutrophil count is 500–1000 cells/mm^3, reduce dose as earlier and resume previous dose when absolute neutrophil count is greater than 1000 cells/mm^3.
            (d) Interrupt dosing for hemoglobin less than 8 g/dL or a reduction of more than 2 g/dL, and restart dosing when hemoglobin normalizes.
            (e) Interrupt therapy if patient experiences a serious infection.
        v. Remission rates in OCTAVE trials
            (a) In OCTAVE 1, 18.5% and 8.2% of patients achieved remission with tofacitinib 10 mg daily and placebo, respectively ($p=0.007$) at 8 weeks.
            (b) In OCTAVE 2, 16.6% and 3.6% achieved remission, respectively ($p<0.001$) at 8 weeks.
            (c) OCTAVE Sustain reported remission at 52 weeks in 34.3% of patients receiving 5 mg of tofacitinib twice daily, 40.6% receiving 10 mg twice daily, and 11.1% receiving placebo ($p<0.001$ both comparisons with placebo).
    b. Upadacitinib (Rinvoq) dosing and outcomes
        i. Induction dosing: 45 mg orally once daily for 8 weeks
        ii. Maintenance dosing: 15 mg orally once daily; 30 mg orally once daily for refractory, severe, or extensive UC.
        iii. Discontinue if response is inadequate following 30 mg maintenance dose.
        iv. Dose adjustments: Use reduced dose of 30 mg daily for induction and 15 mg daily maintenance for the following:
            (a) Creatinine clearance (CrCl) 15–30 mL/min (avoid use in CrCl less than 15 mL/min)
            (b) Child-Pugh class A or B (avoid use in Child-Pugh class C)
            (c) Concurrent strong CYP 3A4 inhibitors.
            (d) Interrupt therapy for severe infection or reduction in absolute neutrophil count less than 1000 cells/mm^3; absolute lymphocyte count less than 500 cells/mm^3; hemoglobin less than 8 g/dL.
        v. In two induction studies (U-ACHIEVE and U-ACCOMPLISH), remission at 8 weeks was achieved with upadacitinib 45 mg daily in 26% and 33% of patients compared with placebo (5% and 4%; $p<0.0001$, both comparisons with placebo). About half the patients enrolled in the trials had experienced failure with at least 1 TNF inhibitor. In the U-ACHIEVE maintenance study, clinical remission at 52 weeks was achieved in 42% with 15 mg daily, 52% with 30 mg daily, and 12% with placebo ($p<0.001$, both comparisons with placebo).

c. Janus kinase (JAK) inhibitor adverse effects
    i. Serious infections include tuberculosis or other opportunistic infections; patients should be screened before starting therapy.
    ii. Lymphocytopenia, neutropenia, and low hemoglobin can occur. Monitor lymphocyte, neutrophil, and hemoglobin concentrations at baseline and periodically during treatment.
    iii. Associated malignancies include lymphomas and lung cancers.
    iv. Other associated adverse effects are higher rates of major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, compared with TNF inhibitors. Current and past smokers appear to be at higher risk. Evaluate the risks and benefits before initiating therapy. Discontinue therapy if a suspected cardiovascular event has occurred.
    iv. Development of deep venous thrombosis, pulmonary embolism, and arterial thrombosis is also associated with JAK inhibitors. Avoid therapy in patients at high risk of thrombosis. Discontinue therapy and evaluate and treat patients with suspected thrombosis.

6. Sphingosine 1-phosphate receptor modulator
    a. Ozanimod (Zeposia)
        i. Indicated in moderate to severe active UC in adults
        ii. Dosing titration: 0.23 mg orally once daily on days 1–4; 0.46 mg orally once daily on days 5–7; then 0.92 mg orally once daily day 8 and thereafter.
        iii. True North Phase III trial showed 18.4% of patients with UC receiving ozanimod and 6% receiving placebo achieved clinical remission at week 10. Of patients who achieved remission who continued with maintenance therapy, 37% receiving ozanimod and 18.5% receiving placebo were in remission at week 52.
        iv. Assessments before initiating ozanimod therapy
            (a) Complete blood count and lymphocyte count
            (b) Electrocardiogram to assess for prolonged QTc, bradycardia, or heart block because ozanimod may reduce heart rate and cause conduction delays liver function tests
            (c) Ophthalmic assessment in patients at risk for macular edema
            (d) Varicella zoster immunity (per vaccination or history of infection) documentation
        v. Contraindications
            (a) Within the past 6 months: myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure
            (b) Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sinoatrial block unless a functioning pacemaker is present
            (c) Severe untreated sleep apnea
            (d) Concurrent monoamine oxidase inhibitor
7. Biologic agents: TNF inhibitors (infliximab, adalimumab, certolizumab, golimumab); integrin inhibitors (natalizumab, vedolizumab); anti-interleukin 12 and anti-interleukin 23 (ustekinumab)
    a. Baseline evaluation before biologic agent use: comprehensive metabolic panel, liver function tests, complete blood cell count; viral hepatitis screening; tuberculosis screening
    b. Infliximab (Remicade)
        i. Chimeric monoclonal antibody against TNFα, intravenous infusion
        ii. Indicated for induction and maintenance of remission in moderate to severe active UC or CD or in fistulizing CD
        iii. Dosing: Moderate to severe active disease or fistulizing disease: 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks; then every 8 weeks as maintenance. Patients who experience a loss of response over time can be treated with a 10 mg/kg dose.
        iv. Therapeutic drug monitoring: Minimal "therapeutic" target trough concentration of infliximab is 7.5 mcg/mL or greater according to the guidelines.

c. Adalimumab (Humira)
   i. Fully humanized antibody to TNFα; therefore, theoretically, the risk of antibody development is reduced
   ii. Indicated for both induction and maintenance therapy for moderate to severe active CD and UC in patients unresponsive to conventional therapy; also indicated for patients who no longer respond to infliximab
   iii. Dosing
      (a) Induction: 160 mg subcutaneously on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg subcutaneously 2 weeks later (day 15)
      (b) Starting on day 29 of therapy, decrease dose to 40 mg subcutaneously every other week (maintenance therapy dose).
   iv. Therapeutic drug monitoring: Minimal "therapeutic" trough concentration of adalimumab is 5 mcg/mL or greater
d. Certolizumab (Cimzia)
   i. Humanized monoclonal antibody fragment to TNFα linked to polyethylene glycol, with murine-complimentary determining regions
   ii. Indicated for maintenance therapy for moderate to severe active CD in patients unresponsive to conventional therapy
   iii. Dosing
      (a) Induction: 400 mg subcutaneously; then 400 mg subcutaneously at weeks 2 and 4
      (b) Maintenance: 400 mg subcutaneously every 4 weeks
   iv. Therapeutic drug monitoring: Evidence is sparse; however, suggested minimal "therapeutic" target trough concentration is 20 mcg/mL or greater.
e. Golimumab (Simponi)
   i. Human IgG1κ monoclonal antibody directed against TNFα
   ii. Indicated for moderate to severe UC in patients intolerant of previous therapies or requiring continuous steroid therapy
   iii. Dosing: 200 mg subcutaneously at week 0, 100 mg at week 2; then 100 mg every 4 weeks thereafter
f. TNF antagonists adverse reactions
   i. Infusion related: hypotension, fever, chills, urticaria, pruritus; infuse over at least 2 hours (may pretreat with acetaminophen and/or antihistamine)
   ii. Delayed hypersensitivity: fever, rash, myalgia, headache, or sore throat 3–10 days after administration.
   iii. Infection: reactivation of latent infections (bacterial, including disseminated tuberculosis, fungal, and sepsis); do not give to patients with active infections. Tuberculosis should be ruled out before any biologic agents are initiated.
   iv. Heart failure exacerbations: contraindicated in New York Heart Association class III/IV heart failure; do not exceed 5-mg/kg dose in other patients with chronic heart failure.
   v. Antibody induction: Up to 50% of patients receiving infliximab may develop antinuclear antibodies; 19% may develop anti-double-stranded DNA antibodies.
   vi. Bone marrow suppression (pancytopenia)
   vii. Black box warning applies to all TNFα antagonists. Unusual cancers have been reported in children and teenage patients taking TNF blockers. Hepatosplenic T-cell lymphoma has occurred mostly in teenaged or young adult males with CD or UC who were taking infliximab and azathioprine or mercaptopurine.
   viii. Hepatitis, with reactivation of hepatitis B virus (HBV) or autoimmune hepatitis; discontinue use if liver function tests increase to more than 5 times the upper limit of normal (ULN).
   ix. Vasculitis with CNS involvement

g. Natalizumab (Tysabri)
    i. Humanized monoclonal antibody that antagonizes integrin heterodimers and inhibits α4 integrin-mediated leukocyte adhesion
    ii. Indicated for induction and maintenance of remission of moderate to severe active CD after an inadequate response to, or intolerance of, conventional therapies and inhibitors of TNFα. John Cunningham (JC) virus serum antibody test should be completed before and every 6 months during natalizumab therapy. Treatment should be discontinued if the result is positive.
    iii. Dosing: Must enroll in the TOUCH program before the drug is dispensed because of its association with progressive multifocal leukoencephalopathy. Induction and maintenance doses are both 300 mg intravenously every 4 weeks. If there is no effect after 12 weeks or an inability to discontinue steroids within 6 months of beginning therapy, discontinue natalizumab.
    iv. Adverse effects: progressive multifocal leukoencephalopathy. Monitor for mental status changes during treatment. Consider magnetic resonance imaging and lumbar puncture if mental status changes or weakness is observed. Monitor for hepatotoxicity, jaundice or other signs of liver disease. Monitor for infection. Observe patients for 1 hour after infusion for infusion reaction. Do not combine with TNFα inhibitors or immunosuppressants.

h. Vedolizumab (Entyvio)
    i. Humanized monoclonal antibody that targets α4β7-integrin–mediated leukocyte adhesion
    ii. Indicated for induction and maintenance of UC and CD after failure of other therapies, including TNFα antagonists.
    iii. Induction and maintenance doses are both 300 mg intravenously given at 0, 2, and 6 weeks and then every 8 weeks. Discontinue if there is no evidence of improvement at 14 weeks.
    iv. Safety profile is similar to natalizumab, with a lower risk of progressive multifocal leukoencephalopathy because the mechanism of vedolizumab is more specific for gut-based integrin; no prescribing program is required for vedolizumab.

i. Ustekinumab (Stelara)
    i. Monoclonal antibody to the p40 subunit of interleukin 12 and interleukin 23 (anti-IL-12/23)
    ii. Indicated for moderate to severely active CD and UC after the failure of corticosteroids, thiopurines, methotrexate, or TNF inhibitors
    iii. Dosing, intravenous:
        (a) Induction dosing is based on weight at week 0: 260 mg for less than 55 kg, 390 mg for more than 55–85 kg, and 520 mg more than 85 kg
        (b) Maintenance dosing: 90 mg subcutaneously every 8 weeks
    iv. Adverse effects
        (a) Common adverse effects: vomiting with induction therapy; nasopharyngitis, injection-site erythema, vulvovaginal candidiasis, bronchitis, pruritus, urinary tract infection, and sinusitis with maintenance treatment
        (b) As with other biologic therapies, serious infections include tuberculosis; therefore, screening for tuberculosis is recommended before starting therapy.

E. Medical management of UC: Treatment is selected according to disease location and severity.
1. Guideline definitions of UC distribution
    a. Distal disease: Distal to splenic flexure (may use oral/systemic or topical [rectal] therapy)
    b. Extensive disease: Proximal to splenic flexure (requires systemic/oral therapy)
2. Mildly active UC
    a. Topical aminosalicylates are recommended for induction of remission for ulcerative proctitis (strong recommendation, high-quality evidence) and left-sided colitis (strong recommendation, moderate-quality evidence). An oral aminosalicylate in combination with a topical aminosalicylate

is more effective than oral therapy alone (conditional recommendation, low-quality evidence). Oral aminosalicylate therapy should be used for mildly active extensive colitis (strong recommendation, moderate-quality evidence).

b. Patients with mildly active UC who are intolerant of or who have responded to aminosalicylate therapy should receive oral budesonide (Uceris) for left-sided disease (strong recommendation, moderate-quality evidence) or systemic corticosteroids for any extent of UC (strong recommendation, low-quality evidence) to induce remission.

c. Continued topical and/or oral aminosalicylate therapy, but not corticosteroids, should be used to maintain remission (strong recommendation, moderate-quality evidence).

3. Moderately to severely active UC
   a. In moderately active UC, oral budesonide is recommended to induce remission (strong recommendation, moderate-quality evidence).
   b. In moderately to severely active UC, systemic steroids, anti-TNF therapy (adalimumab, golimumab, or infliximab), vedolizumab, tofacitinib, or ustekinumab may be used to induce remission. (strong recommendations, moderate to high quality of evidence).
   c. Infliximab for induction of remission should be combined with thiopurine therapy (strong recommendation, moderate-quality evidence for azathioprine).
   d. Patients whose induction with anti-TNF therapy has failed should receive vedolizumab, tofacitinib, or ustekinumab to induce remission (strong recommendation, moderate-quality evidence).
   e. A patient who achieves remission with a biologic agent should be continued on that agent to maintain remission (strong recommendation, moderate-quality evidence). Patients whose remission is achieved using corticosteroids may receive thiopurine therapy to maintain remission (conditional recommendation, low-quality evidence).
   f. Newer oral treatment options (ozanimod and upadacitinib) are indicated for induction and maintenance of remission of moderate to severe active UC in patients for whom TNF antagonist therapy has failed. These agents have not yet been incorporated into treatment guidelines, but can be considered for patients who have experienced failure of the initial treatment options.
4. Hospitalized patients with acute severe UC
   a. Methylprednisolone 40–60 mg/day or the equivalent intravenously is recommended to induce remission (strong recommendation, low-quality evidence).
   b. If a patient's UC does not respond after 3–5 days of intravenous corticosteroid therapy, rescue therapy with infliximab or cyclosporine is recommended (strong recommendation, moderate-quality evidence).
   c. If remission is achieved with infliximab, continue therapy for maintenance. If remission is achieved with cyclosporine, maintain remission with a thiopurine or vedolizumab.

F. Medical management of CD
1. Treatment is selected according to disease location and severity.
2. Mild-moderate active disease: First line for ileal, ileocolonic, or colonic disease
   a. Oral aminosalicylate (mesalamine 3.2–4 g/day or sulfasalazine 6 g/day) is commonly used but considered minimally effective.
   b. Budesonide 9 mg/day is preferred for terminal ileal or ascending colonic disease.
   c. Metronidazole 10–20 mg/kg/day may be used in patients not responding to oral aminosalicylates, but it is generally more effective in patients with perianal or colonic disease.
   d. Ciprofloxacin 1 g/day is considered as effective as mesalamine (generally, second line), but is usually more effective in perianal or colonic disease and is typically used in combination with metronidazole.

3. Moderate-severe disease
    a. Corticosteroids (prednisone 40–60 mg/day or budesonide 9 mg/day if terminal ileal involvement) until resolution of symptoms and resumption of weight gain
    b. Anti-TNFα agents in combination with thiopurines are the preferred therapies for induction of remission for moderate to severe CD. Thiopurine monotherapy or methotrexate is not recommended to induce remission in moderate to severe active CD.
        i. Infliximab 5 mg/kg is an alternative first-line treatment (improvement in up to 80% of patients). Infliximab can be combined with azathioprine in patients whose therapy with aminosalicylates and corticosteroids has failed and who are naive to biologic agents. This combination is superior to each drug given alone; however, there is a risk of hepatosplenic T cell lymphoma.
        ii. Certolizumab 400 mg subcutaneously and then 400 mg subcutaneously at weeks 2 and 4, or adalimumab 160 mg subcutaneously initially followed by 80 mg subcutaneously 2 weeks later, can also be considered, particularly in patients with C-reactive protein values greater than 10 mg/L.
        iii. Adalimumab can be used as initial therapy or for patients who no longer respond to infliximab therapy because they developed antibodies to infliximab.
    c. Vedolizumab 300 mg (or natalizumab) intravenously every 4 weeks can be considered for patients who did not respond to any other conventional medical therapy.
    d. Ustekinumab 260-520 mg intravenously on the basis of patient weight, followed by 90 mg subcutaneously every 8 weeks can be used for patients whose conventional or inhibitor therapy has failed.
    e. Methotrexate maintenance therapy (15–25 mg/week intramuscularly or subcutaneously) is effective in patients whose active disease has responded to intramuscular methotrexate and who have steroid-dependent or steroid-refractory disease.
4. Severe disease
    a. Severe symptoms despite oral corticosteroids or infliximab therapy
    b. Assess need for surgical intervention (mass, obstruction, and abscess).
    c. Administer intravenous corticosteroids (40–60 mg of prednisone equivalent).
    d. Parenteral nutrition may be needed after 5–7 days.
    e. Possibly use intravenous cyclosporine if steroids fail.
5. Maintenance therapy
    a. There is no role for long-term corticosteroid use, but budesonide can be used for up to 3 months in patients with mild-moderate disease with ileal involvement.
    b. Azathioprine/mercaptopurine or infliximab, or the combination, can be used after induction with corticosteroids.
    c. Azathioprine/mercaptopurine or mesalamine (more than 3 g/day) can also be used after surgical resection to prevent recurrence.
    d. Infliximab 5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks or adalimumab 40 mg subcutaneously every other week (starting on day 29 of therapy)
    e. Vedolizumab 300 mg (or natalizumab) intravenously every 4 weeks can be considered for patients who did not respond to conventional medical therapy.
    f. Ustekinumab 90 mg subcutaneously every 8 weeks can be used for patients whose conventional or TNF inhibitor therapy has failed.
    g. Methotrexate intramuscularly 25 mg for up to 16 weeks, followed by 15 mg/week intramuscularly, is effective for patients with chronic active disease.
6. Perianal disease
    a. Simple perianal fistulas (a single tract without abscess and involving less than 30% of the external sphincter; better prognosis; can be treated less aggressively than complex fistulas)
        i. Antibiotics: metronidazole or ciprofloxacin

ii. Azathioprine/mercaptopurine
iii. Infliximab, adalimumab, certolizumab

b. Complex perianal fistulas (involving more than 30% of the external sphincter, multiple tracts, abscess involvement, recurrent fistulas, rectovaginal fistulas; worse prognosis requiring more aggressive therapy than simple fistulas.)
i. Infliximab, adalimumab, or certolizumab in combination with surgery
ii. Antibiotics: Metronidazole or ciprofloxacin (mainly as adjunctive therapy in this case)
iii. Azathioprine/mercaptopurine or methotrexate

Patient Cases

4. A 35-year-old man presents with newly diagnosed mildly active UC affecting his descending colon and rectum (left-sided disease). He takes loratadine 10 mg/day for seasonal allergies. He has no known drug allergies. Which drug regimen is best?
   A. Balsalazide 750 mg twice daily.
   B. Methotrexate 25 mg intramuscularly once weekly.
   C. Infliximab 5 mg/kg intravenously.
   D. Mesalamine enema 4000 mg rectally once daily.

5. A 25-year-old woman (height 62 inches, weight 50 kg) presents to the clinic with a 12-week history of cramping abdominal pain, fever, fatigue, and 3 or 4 bloody stools per day. A colonoscopy reveals patchy inflammation in the colon and terminal ileum consistent with moderately active CD. She has an allergy to penicillin (rash). Vital signs include body temperature 98°F, heart rate 100 beats/minute, respiratory rate 18 breaths/minute, and blood pressure 118/68 mm Hg. Which therapeutic choice is best?
   A. Mesalamine (Pentasa) 1000 mg four times daily.
   B. Infliximab (Remicade) 275 mg intravenously and azathioprine 100 mg daily.
   C. Budesonide (Entocort) 9 mg orally once daily.
   D. Adalimumab (Humira) 40 mg subcutaneously every 2 weeks.

V. COMPLICATIONS OF LIVER DISEASE

A. Severity of liver disease is assessed using scoring tools such as the Chuld-Turcotte-Pugh or model for end-stage liver disease (MELD) scores (Tables 12 and 13).

Table 12. Child-Turcotte-Pugh Classification of the Severity of Cirrhosis

Variable	Score		
	1 Point	2 Points	3 Points
Encephalopathy	Absent	Mild-moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds above normal)	1–4	4–6	>6

[a]Class A = total score of 5 or 6; class B = total score of 7–9; class C = total score of 10 or more.

Table 13. Model for End-Stage Liver Disease (MELD)

Version	Calculation	Comments
Original	9.57 × ln(creatinine) + 3.78 × ln(total bilirubin) + 11.2 × ln(INR) + 6.43	Score ranges from 6 to 40 Higher number indicates more severe disease Used to predict mortality and prioritize patients for liver transplantation
MELD-Na	MELD − Na − [0.025 × MELD × (140 − Na)] + 140	Incorporates sodium May better discriminate risk of death
UNOS modification	Original MELD equation with limits set on laboratory values that are entered	Lower end of laboratory values for SCr, bilirubin, and INR are set at 1 with a maximum of 4 If two or more dialysis treatments within the prior week or within 24 hr of CVVHD within the prior week, SCr concentration automatically set to 4.0 mg/dL

CVVHD = continuous venovenous hemodialysis; INR = international normalized ratio; MELD = model for end-stage liver disease; Na = sodium, UNOS = United Network for Organ Sharing.

B. Ascites
   1. Definition: Free fluid in the abdominal cavity owing to increased resistance within the liver (forces lymphatic drainage into the abdominal cavity) and reduced osmotic pressure within the bloodstream (hypoalbuminemia); develops at a 5-year cumulative rate of 30% in compensated liver disease
   2. Clinical features: protuberant abdomen, shifting dullness, fluid wave, bulging flanks, abdominal pain
   3. Diagnosis
      a. Clinical features
      b. Abdominal ultrasonography
      c. Paracentesis, use to determine serum-ascites albumin gradient (SAAG), calculated by subtracting the ascites albumin concentration from the serum albumin concentration; a value greater than 1.1 indicates ascites caused by portal hypertension
   4. Treatment
      a. Treat the underlying cause of cirrhosis. Improvement in cirrhosis may result in improved ascites.
      b. Attainment of negative sodium balance
         i. Dietary sodium restriction (<2000 mg/day), fluid restriction (<1.5 L/day) if serum sodium is less than 120–125 mmol/L
         ii. Goal is sodium excretion greater than 78 mmol/day. A random spot urine sodium concentration greater than the potassium concentration (ratio greater than 1) correlates with a 24-hour sodium excretion of greater than 78 mmol/day with 90% accuracy.
         iii. Diuretics
            (a) Spironolactone alone may be sufficient for an initial episode of ascites. Combined spironolactone 100 mg and furosemide 40 mg may be necessary for subsequent episodes. Dose titration up to 400 mg of spironolactone and 160 mg of furosemide may be necessary; maintenance of the initial ratio is not required, but the ratio should be adjusted based on potassium, blood pressure, and urine output. Dose increases of spironolactone should be made every 72 hours to account for its onset of action. Patients who develop gynecomastia with spironolactone may respond to eplerenone or amiloride. Spironolactone 100 mg is considered equivalent to eplerenone 50 mg or amiloride 10 mg. Patients who do not achieve adequate diuresis with furosemide may respond to bumetanide or torsemide.
            (b) If tense ascites is present, large-volume paracentesis (>5 L removed) can be used. Administer albumin at a dose of 6–8 g/L of ascitic fluid removed if more than 5 L is removed at one time.

iv. No upper limit of weight loss if massive edema is present, 0.5 kg/day in patients without edema
v. Monitor for electrolyte imbalances, renal impairment, and gynecomastia (spironolactone).

c. Discontinue drugs associated with sodium/water retention, such as NSAIDs. Avoid angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to prevent renal failure.

C. Hepatic encephalopathy

1. Definition: Hepatic encephalopathy is brain dysfunction caused by liver insufficiency or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.
   a. Thought to be secondary to the accumulation of nitrogenous substances (mainly NH_3) arising from the gut. Overall, NH_3 serum concentrations do not correlate well with mental status
   b. Other theories are related to the activation of γ-aminobutyric acid receptors by endogenous benzodiazepine-like substances, possible zinc deficiency, or altered cerebral metabolism.
2. Clinical features and criteria
   a. Can result in acute encephalopathy with altered mental status and progress to coma if untreated; asterixis ("hand flap") is a classic physical finding
   b. May be precipitated by various factors including constipation, GI bleeding, infection, hypokalemia, dehydration, hypotension, and CNS-active drugs (benzodiazepines and narcotics)
   c. The West Haven Criteria and the Glasgow Coma Scale are used to classify and grade; see Table 14.

Table 14. Common Criteria and Clinical Symptoms for Hepatic Encephalopathy

West Haven Criteria	ISHEN	Clinical Description
Unimpaired		No current or history of encephalopathy
Minimal	Covert	Psychometric or neuropsychologic alterations of tests exploring psychomotor speed and executive functions or neurophysiologic alterations without clinical evidence of mental change
Grade I		Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm
Grade II	Overt	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis
Grade III		Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
Grade IV		Coma

ISHEN = International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

3. Classifications
    a. Subtypes according to underlying disease
        i. Type A: Owing to acute liver failure
        ii. Type B: Owing to portosystemic bypass or shunting
        iii. Type C: Owing to cirrhosis
    b. Duration
        i. Episodic
        ii. Recurrent (occurs within a time frame of 6 months or less)
        iii. Persistent: Denotes a pattern of behavioral alteration that is always present and interspersed with relapses of overt hepatic encephalopathy
    c. Presence or absence of precipitating factors
4. Treatment
    a. Assess need for airway support and remove possible precipitating factors.
    b. Main treatments targeted at reducing the nitrogen load in the gut.
    c. Treatment recommendations are based on type C (Table 15).

Table 15. Treatment of Hepatic Encephalopathy Owing to Cirrhosis (Type C)

Type	Recommendations
Episodic overt HE (type C)	Treat episodic overt HE and then use secondary prophylaxis
	Primary prophylaxis is not indicated unless cirrhosis and high risk for HE
	Lactulose is first-line treatment for overt HE
	Rifaximin can be used as add-on therapy with lactulose to prevent recurrence after the second episode of overt HE
	Oral BCAA can be used as alternative or additional therapy in patients unresponsive to traditional therapies
	Neomycin or metronidazole can be used as alternative treatment

BCAA = branched chain amino acids; HE = hepatic encephalopathy; IV = intravenous.

    d. Lactulose
        i. Nonabsorbable disaccharide: Metabolized by colonic bacteria to acetic and lactic acid. NH_3 present in the GI lumen is reduced to ammonium ion (NH_4^+) through the reduction in pH ("ammonia trapping") and is unable to diffuse into the bloodstream. Lactulose can also alter bacterial metabolism, resulting in increased uptake of NH_3.
        ii. Dose: 45 mL orally every 1–2 hours until the patient has a loose bowel movement and then titrate to two or three loose bowel movements per day (typically, 15 to 45 mL two or three times daily); may also administer as an enema (300 mL plus 700 mL of water retained for 1 hour). Powder formulation (Kristalose) is available in 10- and 20-g packets to be dissolved in 120 mL water (10 g = 15 mL traditional lactulose). This formulation is more palatable than traditional syrup.
        iii. Can be continued long term to prevent recurrent encephalopathy
        iv. Flatulence, diarrhea, and abdominal cramping are common adverse effects.
    e. Antibiotics
        i. Targeted at reducing the number of intraluminal urease-producing bacteria that can lead to excess NH_3 production
        ii. Neomycin (3–6 g/day in three or four divided doses for 1–2 weeks and then 1–2 g/day maintenance) or metronidazole (250 mg orally twice daily) can be used; neomycin is considered as effective as lactulose.

iii. From 1% to 3% of neomycin is absorbed. Caution is required for with long-term use with renal insufficiency. Long-term metronidazole can result in peripheral neuropathy.
iv. Rifaximin is as effective as lactulose and other nonabsorbable antibiotics, and it may be better tolerated. The approved dose for reduction in overt encephalopathy in patients 18 years and older is 550 mg twice daily. Drug cost may be greater, but this may be offset by fewer hospitalizations and shorter lengths of stay. Previous studies in the short-term setting have used 400 mg three times daily.

f. Other possible treatments
i. Polyethylene glycol 3350 4 L given orally or by nasogastric tube over 4 hours resulted in faster improvement in encephalopathy than lactulose.
ii. Benzodiazepine antagonists such as flumazenil can be used in cases of possible benzodiazepine overdose; however, the risk of lowering the seizure threshold often limits their use.
iii. Zinc supplementation should be used in patients with documented zinc deficiency.
iv. Nutritional interventions include 35–40 kcal/kg/day based on IBW and 1.2–1.5 g/kg/day protein intake

D. Gastroesophageal varices
1. Background
a. Resistance to blood flow within the liver caused by cirrhosis results in portal hypertension. Collateral blood vessels (e.g., esophageal varices) are formed because of this increased resistance to blood flow.
b. Variceal hemorrhage can occur in 25%–35% of patients with cirrhosis and varices; mortality rates are as high as 30%–50% per bleed; recurrence rates are as high as 70% within the first 6 months after an initial bleed.
2. Management of acute variceal bleeding
a. Fluid resuscitation and hemodynamic stabilization. Maintain hemoglobin concentration of about 8 g/dL. Administration of fresh frozen plasma or platelets can be considered for patients with considerable coagulopathy.
b. Endoscopy to provide assessment and possible intervention
i. Sclerotherapy stops bleeding in 80%–90% of patients; it may be associated with complications such as perforation, ulceration, stricture, and bacteremia. Possible sclerosing agents are ethanolamine and sodium tetradecyl sulfate.
ii. Endoscopic variceal band ligation can be used as an alternative to sclerotherapy, with fewer complications.
c. Medical management of acute variceal bleeding
i. Institute after fluid resuscitation (before endoscopy, if possible)
ii. Most therapies are targeted at reducing splanchnic blood flow and portal pressure; a combination of endoscopic and vasoactive therapies is most effective.
iii. Somatostatin analog: Octreotide
(a) Prevents postprandial hyperemia by reducing portal pressure (by reduced splanchnic blood flow) through inhibitory effects on vasoactive peptides such as glucagon, or by a local vasoconstrictor effect
(b) Preferred agent in combination with endoscopic interventions because of more favorable adverse effect profiles; main adverse effects include hyperglycemia and abdominal cramping
(c) Dosing: 50-mcg intravenous bolus, then 50 mcg/hour intravenously for 3–5 days

iv. Vasopressin: 0.2–0.4 unit/minute plus nitroglycerin 40–400 mcg/minute for 3–5 days
  (a) Vasopressin use results in splanchnic vasoconstriction; it is used less often secondary to the need for both drugs and coronary vasoconstriction/ hypertension with vasopressin (nitroglycerin attenuates these effects to some extent).
  (b) Vasopressin has a worse adverse effect profile than octreotide. Risk of ischemia, hypotension, and skin necrosis limit use.

v. Nondrug measures to control bleeding
  (a) Typically used for medically unresponsive bleeding
  (b) Minnesota or Blakemore tube: Balloon compression applied directly to bleeding varices
  (c) Transjugular intrahepatic portosystemic shunt results in shunting of blood from the portal circulation; this may be associated with complications such as bleeding, infection, and increased risk of hepatic encephalopathy
  (d) Surgery

vi. Antibiotic therapy
  (a) The use of oral or intravenous prophylactic antibiotics in patients with cirrhosis with variceal bleeding reduces short-term mortality; these agents should be prescribed.
  (b) Typical regimens include ceftriaxone intravenously 1 gram/day for 7 days, especially when quinolone-resistant bacteria are prevalent or the patient has been receiving quinolone prophylaxis. Fluoroquinolone can be considered in patients who do not have a high risk of quinolone resistance.

d. Prevention of variceal bleeding

i. Primary prophylaxis
  (a) A screening esophagogastroduodenoscopy is recommended to evaluate for esophageal and gastric varices when the diagnosis of cirrhosis is made.
  (b) Pharmacologic therapy is not recommended to prevent the development of varices in patients with cirrhosis who have not yet developed varices.
  (c) Patients who have small varices and no history of bleeding, but meet the criteria for increased risk of bleeding (Child-Pugh class B or C, red wale marks on varices), should receive preventive drug therapy with nonselective β-blockers.
  (d) Nonselective β-blockers can be considered; however, the long-term benefit is unclear in patients who have small varices and no history of bleeding, but who do not meet the criteria for increased risk of bleeding.
  (e) Nonselective β-blockers are indicated in all patients with medium or large varices and no history of bleeding. An endoscopic variceal ligation (EVL) can be used if nonselective β-blockers are contraindicated.
  (f) Mechanism of nonselective β-blockers: Blockade of β_1-receptors reduces cardiac output, whereas blockade of β_2-receptors prevents splanchnic vasodilation; unopposed α_1-mediated constriction of the splanchnic circulation also leads to reductions in portal pressure.
  (g) Therapy should aim for a resting heart rate of 55–60 beats/minute or a 25% reduction from baseline. Based on available data, a reduction in hepatic-vein pressure gradient (HVPG) of at least 10% for primary prophylaxis and at least 20% for secondary prophylaxis constitutes β-blocker response.
  (h) Nonselective β-blockers (propranolol, nadolol, carvedilol) are associated with a significant reduction in the incidence of first bleed.

(i) Long-acting nitrates (isosorbide mononitrate or dinitrate) should not be used for primary prophylaxis. These agents are believed to decrease intrahepatic resistance and are considered as effective as propranolol; however, there is an increased incidence of mortality in some studies when they are used as monotherapy.
(j) Shunt surgery or endoscopic sclerotherapy should not be used for primary prophylaxis.

ii. Secondary prophylaxis
(a) All patients with a history of variceal bleeding should receive secondary prophylaxis to prevent recurrent bleeding.
(b) A combination of endoscopic variceal band ligation and nonselective β-blockers is considered the most effective regimen.
(c) Nonselective β-blockers are associated with approximately a 20% reduction in the incidence of variceal rebleeding; reductions in mortality are minimal and inconsistent between trials. Most studies are of patients with Child-Turcotte-Pugh class A or B cirrhosis; class C patients may be unable to tolerate β-blockers.
(d) Combining nonselective β-blockers with nitrates leads to slightly higher reductions in rebleeding rates; no added mortality benefit is observed, and there is a higher incidence of adverse effects with the combination.
(e) Sclerotherapy is no longer recommended for secondary prophylaxis because EVL has been shown to be better, with fewer complications.
(f) The transjugular intrahepatic portosystemic shunt is highly effective at preventing recurrent bleeding; however, it is associated with a 30%–40% incidence of encephalopathy and is reserved for medically unresponsive patients.
(g) Contraindications to nonselective β-blockers: asthma, insulin-dependent diabetes with frequent hypoglycemia, peripheral vascular disease
(h) Adverse effects of nonselective β-blockers: light-headedness, fatigue, shortness of breath, sexual dysfunction, bradycardia
(i) Adverse effects of EVL: transient dysphagia, chest discomfort

E. Spontaneous bacterial peritonitis (SBP)
1. Background
a. Definition: SBP is the infection of previously sterile ascitic fluid without an apparent intra-abdominal source; it is considered primary, as opposed to secondary, peritonitis.
b. May be present in 10%–30% of hospitalized patients with cirrhosis and ascites
c. Associated with 20%–40% of in-hospital mortality; poor prognosis after recovery, with 2-year survival after initial episode reported at about 30%
2. Pathophysiology
a. Principal theory is seeding of the ascitic fluid from an episode of bacteremia.
b. The bacteria present are usually enteric pathogens; thus, they may enter the blood because of increases in gut permeability secondary to portal hypertension, suppression of hepatic reticuloendothelial cells, or translocation of the gut wall and dissemination through the mesenteric lymph system.
c. Reduced opsonic activity of the ascitic fluid and alterations in neutrophil function may also be contributing factors.
d. Most SBP infections are monobacterial. About 60% are caused by gram-negative bacteria such as Escherichia coli or Klebsiella spp. Recently, there has been an increase in gram-positive organisms (e.g., *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp.) and multidrug-resistant organisms, especially in the setting of nosocomial or health-care associated SBP.

Table 16. Recommended Empiric Antiobiotic Regimens for SBP

Community-Acquired SBP	Nosocomial SBP or Risk Factors for MDRO
Third-generation cephalosporin: cefotaxime or ceftriaxone	Piperacillin-Tazobactam +/– Vancomycin (if prior infection or MRSA-positive surveillance swab) —OR— Daptomycin if prior infection or VRE-positive surveillance swab —OR— Meropenem (if current or recent exposure to piperacillin-tazobactam or known MDRO) +/– Glycopeptide (vancomycin or teicoplanin) if MRSA risk

MDRO = multidrug-resistant organism; MRSA = methicillin-resistant *Staphylococcus aureus*; SBP = spontaneous bacterial peritonitis; VRE = vancomycin-resistant enterococcus.

3. Clinical and laboratory features
    a. Clinical presentation can vary. About one-third of patients present without symptoms. Common symptoms include fever, abdominal pain, nausea, vomiting, diarrhea, rebound tenderness, and exacerbation of encephalopathy. About 33% of patients present with renal failure, which is associated with significant increases in mortality. GI bleeding and septic shock or hypotension rarely occur.
    b. Laboratory
        i. May see systemic leucocytosis or increases in SCr
        ii. Abdominal paracentesis must be performed. Paracentesis and ascitic fluid cultures must be taken before the first dose of empiric antibiotics is administered.
            (a) The presence of more than 250 polymorphonuclear cells/mm^3 is diagnostic for SBP.
            (b) Lactate dehydrogenase, glucose, and protein values may help to distinguish it from secondary peritonitis.
4. Treatment of acute SBP
    a. Because of the high associated mortality, treatment should be initiated promptly in patients with clinical and laboratory features consistent with SBP.
    b. Predictors of poor outcomes include bilirubin greater than 8 mg/dL, albumin less than 2.5 g/dL, creatinine greater than 2.1 mg/dL, hepatic encephalopathy, hepatorenal syndrome, and upper GI bleeding.
    c. Antibiotic therapy plus albumin if patient meets criteria for albumin use (see below)
        i. Empiric therapy targeting likely organisms should be instituted as soon as possible after paracentesis and culture.
        ii. Empiric antibiotic recommendations are listed in Table 16.
        iii. Treatment duration: 5–7 days;
    d. Albumin
        i. Rationale: The hemodynamics of patients with cirrhosis reflect a state of intravascular hypovolemia and organ hypoperfusion; SBP is thought to exacerbate this effect, resulting in progressive renal hypoperfusion and precipitation of renal failure or hepatorenal syndrome.
        ii. Albumin infusion improves survival in patients with cirrhosis and SBP. Patients with jaundice and/or acute kidney injury at the time of SBP diagnosis benefit most from albumin infusion.
        iii. Albumin dosing: 1.5 g/kg on admission; 1 g/kg on hospital day 3
        iv. Guidelines suggest using this albumin regimen with antibiotics if SCr > 1 mg/dL, BUN > 30 mg/dL, or total bilirubin > 5 mg/dL.

5. Prevention
    a. Prophylactic oral antibiotics are used to reduce the number of enteric organisms in the GI tract (GI decontamination), with the hope of reducing the chance of bacterial translocation to prevent SBP in high-risk patients.
    b. Antibiotic regimens are similar for both primary and secondary prevention:
        i. Fluoroquinolones: ciprofloxacin
        ii. Trimethoprim/sulfamethoxazole
    c. Primary prevention
        i. During acute upper GI bleeding, give 7-day course of ceftriaxone during hospitalization.
        ii. Can also consider indefinite antibiotic prophylaxis in select patients with ascitic fluid protein concentration < 1.5 g/dL and renal dysfunction or liver failure present (SCr > 1.2 mg/dL, BUN > 25 mg/dL, sodium < 130 mg/dL, or Child-Turcotte-Pugh score > 9 with bilirubin > 3 mg/dL).
        iii. Norfloxacin is the most studied, but is not available in the United States. Use a comparable fluoroquinolone or trimethoprim/sulfamethoxazole for primary prevention.
    d. Secondary prevention
        i. All patients recovering from an initial episode of SBP should be treated with oral prophylactic antibiotics indefinitely.
        ii. Consider patient for liver transplantation because 2-year survival is 25%–30% after recovery.

F. Hepatorenal syndrome
1. Criteria in patients with cirrhosis and ascites: SCr > 1.5 mg/dL, no improvement in SCr to less than 1.5 mg/dL after withdrawal of diuretics and administration of albumin, absence of shock, no current nephrotoxins, absence of parenchymal kidney disease and microhematuria, and a normal renal ultrasound
2. Subtypes
    a. Type 1: Doubling of SCr to greater than 2.5 mg/dL or a 50% reduction in CrCl to less than 20 mL/minute/1.73 m^2 in less than 2 weeks
    b. Type 2: Nonrapid progression of worsening of renal function. Associated with high mortality.
3. Treatment: Vasoconstrictor therapy along with albumin is recommended. Norepinephrine infusion in the intensive care unit is preferred. Oral midodrine combined with octreotide may be considered in patients who are unable to receive norepinephrine.

G. Alcoholic liver disease
1. Subset of chronic liver disease. Patients may develop steatosis and eventually progress to cirrhosis. About 10%–35% of patients may develop severe alcoholic hepatitis.
2. Prognosis of alcoholic hepatitis may be initially evaluated by the Maddrey discriminant function (MDF) score, calculated as 4.6 × (Patient's PT − Control PT) + Total bilirubin (mg/dL), where PT is prothrombin time. Patients whose score is greater than 32 have a poor prognosis. Patients with a MELD score greater than 20 should also be considered for drug therapy.
    a. Patients with an MDF greater than 32, with or without encephalopathy, or a MELD score greater than 20 should be considered for a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper. This may lead to a 30% decrease in the risk ratio of short-term death. A Lille score calculation, which is a dynamic measure that considers the change in bilirubin, should be assessed after 7 days of corticosteroid therapy to determine whether improved laboratory findings warrant continuation of the corticosteroid course for the full 28 days.
    b. Intravenous acetylcysteine in combination with corticosteroids should be considered depending on survival benefit and reduction in early complications (infection, hepatorenal syndrome) compared with corticosteroid therapy alone.
    c. Pentoxifylline therapy is no longer recommended for alcoholic hepatitis.

Patient Cases

6. A 47-year-old woman with a history of alcoholic cirrhosis (Child-Turcotte-Pugh class C) is admitted to the hospital with nausea, abdominal pain, and fever. Physical examination reveals a distended abdomen with shifting dullness, a positive fluid wave, and the presence of diffuse rebound tenderness. She also has 1+ lower extremity edema. Current medications include furosemide 80 mg twice daily and spironolactone 200 mg once daily. A diagnostic paracentesis reveals turbid ascitic fluid, which was sent for culture. Laboratory analysis of the fluid revealed an albumin concentration of 0.9 g/dL and the presence of 1×10^3 white blood cells (45% polymorphonuclear neutrophils). Serum laboratory studies reveal SCr 1.2 mg/dL, BUN 37 mg/dL, AST 60 IU/mL, ALT 20 IU/mL, serum albumin 2.5 g/dL, and total bilirubin 3.2 mg/dL. What is the best course of action?
   A. Initiate intravenous albumin and await culture results.
   B. Initiate intravenous vancomycin plus tobramycin.
   C. Initiate intravenous cefotaxime plus albumin therapy.
   D. Initiate oral trimethoprim/sulfamethoxazole double strength.

7. A 56-year-old man with a history of Child-Turcotte-Pugh class B cirrhosis secondary to alcohol abuse is admitted with a 2-day history of confusion, disorientation, somnolence, and reduced oral intake. On examination, he is afebrile, with abdominal tenderness, reduced reflexes, dry mucous membranes, and asterixis. Paracentesis is negative for infection. He takes propranolol 40 mg three times daily. Which recommendation is best for treating this patient's hepatic encephalopathy?
   A. Initiate rifaximin 550 mg orally twice daily.
   B. Initiate lactulose 30 mL orally every 2 hours.
   C. Initiate polyethylene glycol 3350 17 g orally twice daily.
   D. Initiate ceftriaxone 1 g intravenously daily.

VI. VIRAL HEPATITIS

A. Definitions: For all hepatitis virus infections, acute hepatitis is defined as infection for less than 6 months, whereas chronic infection is infection for more than 6 months.

B. HAV
   1. Background
      a. An RNA virus that is associated with the development of self-limited hepatitis
      b. Transmission occurs mainly through the fecal–oral route.
         i. Areas of poor sanitation; also flooding leading to increased spread
         ii. Foodborne: shellfish, water, milk, vegetables
         iii. Person-to-person contact: sexual, day care, intravenous drug use, household, restaurant workers
         iv. The Centers for Disease Control and Prevention (CDC) tracks HAV outbreaks. As of November 2021, 22 states report ongoing outbreaks, and 15 states report recently ended outbreaks. The CDC recommends vaccination for prevention of infection (www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm#anchor_1614015686).
      c. After exposure, incubation for 14–50 days occurs; patients may have general, nonspecific symptoms such as nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, and jaundice.
      d. Most patients have self-limited disease lasting less than 2 months; death of the hepatocyte results in elimination of the virus.
      e. HAV is associated with very low mortality (less than 1%) and is not associated with the development of chronic hepatitis. Fulminant hepatitis can occur in some instances.

2. Diagnosis
    a. Clinical signs and symptoms include nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Some patients may have mild asymptomatic disease.
    b. Recent possible exposures
    c. Laboratory data
        i. IgM antibody to HAV (anti-HAV) is detectable in the serum 5–10 days before the onset of symptoms. Once the infection clears, the IgM antibody is replaced by IgG antibodies during a 2- to 6-month period. These antibodies confer lifelong protective immunity against subsequent infection.
        ii. Elevation of aminotransferases
    d. Management of acute HAV infection is mainly supportive; avoid hepatotoxic medications, such as acetaminophen.
3. Preexposure prophylaxis
    a. Active (vaccination) or passive (immune globulin) prophylaxis can be used.
    b. Havrix (GlaxoSmithKline) and Vaqta (Merck) are the two available HAV vaccines; Twinrix is a combination HAV and HBV product (GlaxoSmithKline).
    c. Populations requiring preexposure prophylaxis with HAV vaccine
        i. All children older than 1 year
        ii. People experiencing homelessness
        iii. International travelers
        iv. Men who have sex with men
        v. Injection or non-injection drug users
        vi. People with occupational risk of exposure
        vii. Patients with chronic liver disease or human immunodeficiency virus (HIV) infection
        viii. Pregnant women at risk for HAV infection or severe outcome from HAV infection
        ix. People who have close personal contact with international adoptee
    d. Populations requiring preexposure prophylaxis with HAV immune globulin
        i. Travelers to endemic countries
        ii. Children younger than 1 year (vaccine not approved for this age group)
        iii. Doses: 0.1 mL/kg for travel up to 1 month, 0.2 mL/kg for travel up to 2 months, 0.2 mL/kg every 2 months for travel longer than 2 months. Administer intramuscularly.
4. Postexposure prophylaxis
    a. Immune globulin can be given at a dose of 0.1 mL/kg intramuscularly within 2 weeks of exposure. HAV vaccine is recommended in patients 12 months to 40 years old who are otherwise healthy. Patients older than 40 should receive the vaccine with or without concurrent immune globulin administration. Patients 12 months and older who are immunocompromised or who have chronic liver disease should receive both the vaccine and immune globulin.
    b. Offer to those not previously vaccinated in the following situations:
        i. Close personal contact with a documented infected person
        ii. Staff or attendees of day care centers if one or more cases are recognized in children or employees or if cases are recognized in two or more households of attendees
        iii. Common source of exposures
            (a) If a food handler receives a diagnosis of HAV, vaccine or immune globulin should be administered to other food handlers at the same establishment. Administration of HAV vaccine or immune globulin to patrons typically is not indicated, but may be considered if:
                (1) The food handler was probably infectious, and he or she both directly handled uncooked or cooked food and had diarrhea or poor hygienic practices.
                (2) Patrons can be identified and treated in 2 weeks or less after exposure.

(b) In settings where repeated exposures to HAV might have occurred, stronger consideration of HAV vaccine or immune globulin use could be warranted. In a common-source outbreak, postexposure prophylaxis should not be provided to exposed individuals after cases have begun to occur, because the 2-week period after exposure during which immune globulin or HAV vaccine is known to be effective will have been exceeded.

C. HBV
1. Background
   a. HBV is a DNA virus; there are more than 350 million infected patients worldwide.
   b. Transmission routes
      i. Parenteral: intravenous drug abuse, needlestick, transfusion, ear or body piercing
      ii. Bodily fluids: saliva, semen, vaginal fluid
      iii. Sexual contact: heterosexual and homosexual
      iv. Perinatal: mother to child at birth
   c. Associated with both acute and chronic disease. Natural history of HBV is age dependent. Risk of developing chronic infection after an acute infection is 90% in neonates, 30% in children younger than 5 years, and 2%–6% in adults.
   d. Chronic infection with HBV increases the risk of hepatocellular carcinoma.
   e. Diagnosis
      i. Clinical signs and symptoms: nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, jaundice (30% may have no symptoms)
      ii. Serologic diagnosis (Table 17)
      iii. Combinations of serologic markers must be reviewed to distinguish acute from chronic infections.
      iv. Eight different HBV genotypes (A–H) exist. Routine genotype testing is not endorsed by the guidelines.

Table 17. HBV Serologies

Serologic Marker	Abbreviation	Comment
Surface antigen	HBsAg	First detectable serum antigen during acute infection; also present in chronic infection
Core antigen	HBcAg	Present early after cell damage during acute infection; typically cannot measure this in the serum
E antigen	HBeAg	Denotes ongoing active viral replication
Anti–surface antigen antibody	Anti-HBs	Confers protective immunity; present after recovery from acute infection or after vaccination
Anticore antigen antibody (IgM)	IgM Anti-HBc	Present in acute infection
Anticore antigen antibody (IgG)	Anti-HBc	Appears at onset of symptoms Denotes prior exposure to HBV Cannot use in isolation to distinguish acute from chronic infection
Anti-E antibody	Anti-HBe	May indicate peak replication has passed
HBV DNA	HBV DNA	Marker of active HBV replication

HBcAg = hepatitis B core antigen; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Ig = immunoglobulin.

(a) Most patients have hepatitis B envelope antigen (HBeAg)-positive disease.
(b) HBeAg-negative disease: Mutation in the precore or core promoter regions. These variants are known as precore mutants; these mutations do not allow monitoring of loss of E antigen as a clinical marker of suppressed replication. Monitor reduction in HBV DNA; patients infected with these variants also tend to have lower serum HBV DNA and fluctuating liver function tests.
(c) Centers for Disease Control and Prevention guidelines for screening for HBV infection indicate that the serologic assay for HBV surface antigen (HBsAg) should be the serologic screening test used for the following populations. Additional HBV tests are needed in combination with the HBsAg for select populations as listed below.
    (1) People born in geographic regions with HBsAg prevalence greater than 2% regardless of vaccination history
    (2) Men who have sex with men; also test for anti-HBc or anti-HBs
    (3) Past or current intravenous drug users; also test for anti-HBc or anti-HBs
    (4) Patients receiving cytotoxic chemotherapy or immunosuppressive therapy related to organ transplantation or rheumatologic or GI disorders. In addition, test for anti-HBc or anti-HBs.
    (5) U.S.-born people not vaccinated as infants whose parents were born in regions with HBV endemicity greater than 8%
    (6) People with elevated ALT and AST of unknown etiology
    (7) Donors of blood, plasma, organs, tissues, or semen. In addition, test for anti-HBc and HBV DNA.
    (8) Pregnant women (during each pregnancy, preferably in the first trimester)
    (9) Infants born to HBsAg-positive mothers
    (10) Household, needle sharing, or sex contacts of people known to be HBsAg positive. In addition, test for anti-HBc or anti-HBs.
    (11) People who are the sources of blood or bodily fluid for exposures that might require postexposure prophylaxis
    (12) People who are living with HIV. In addition, test for anti-HBc or anti-HBs.

v. Clinical definitions (Table 18)

Table 18. Clinical Definitions of HBV

Chronic HBV Infection	Inactive HBV Carrier State
HBsAg positive > 6 mo Serum HBV DNA 20,000 IU/mL (105 copies/mL), lower values 2000–20,000 IU/ mL (104–105 copies/mL) are often observed in HBeAg-negative chronic HBV Persistent/intermittent elevation of AST and ALT Chronic hepatitis and moderate-severe necroinflammation on biopsy	HBsAg positive > 6 mo HBeAg negative, anti-HBeAg positive Serum HBV DNA < 2000 IU/mL (104 copies/mL) Persistently normal AST and ALT; absence of significant hepatitis on biopsy

ALT = alanine aminotransferase; AST = aspartate aminotransferase

2. Treatment of chronic infection
    a. Treatment recommendations
        i. Patients who are HBeAg positive with elevated ALT concentrations and compensated liver disease should be observed for 3−6 months for spontaneous conversion from HBeAg positive to anti-HBe (or HBeAb positive) indicating seroconversion, before initiating treatment. Antiviral treatment should be considered in patients whose ALT remains greater than 2-fold the ULN and whose HBV DNA is greater than 20,000 IU/mL.
        ii. Patients who are HBeAg negative with positive anti-HBe, normal ALT, and HBV < 2000 IU/mL should be monitored every 3 months for 1 year and then every 6–12 months if they remain in the inactive carrier state.
    b. Patients who meet the criteria for chronic infection should be treated. Choice of initial therapy is based on patient profile, prior treatments, contraindications to drug therapy, and medication and monitoring costs.
    c. Monitoring for efficacy should be based on the following responses:
        i. Biochemical: Reduction of liver function tests to within the normal range
        ii. Virologic: Reduction of HBV DNA to undetectable concentrations and loss of HBeAg if HBeAg positive
            (a) A primary nonresponse is considered a decrease in HBV DNA of less than 2 log/mL after at least 24 weeks of therapy. Patients who do not meet these criteria should receive an alternative treatment.
            (b) Response should be assessed by reductions in HBV DNA for HBeAg-negative patients.
3. Drug therapies
    a. Reverse transcriptase inhibitors
        i. In general, lamivudine and telbivudine are not preferred as first-line therapies because of high rates of resistance.
        ii. All reverse transcriptase inhibitors carry a black box warning for the development of lactic acidosis and severe hepatomegaly with steatosis. Monitor for worsening liver function tests, and periodically assess renal function. Female and obese patients are at higher risk. Reductions in bone mineral density (BMD) have been associated with long-term use. Assess baseline BMD in patients older than 12 years with a history of pathologic fracture or osteoporosis.
        iii. Tenofovir, disoproxil fumarate, and entecavir are preferred antivirals in HBV with decompensated cirrhosis, where they are safer than pegylated interferon and have higher potency and minimal risk of resistance compared with other antivirals.
        iv. Entecavir (Baraclude)
            (a) Indicated for HBeAg-negative and HBeAg-positive patients with persistently elevated AST or ALT or histologically active disease; effective in lamivudine-resistant YMDD mutants
            (b) Reduces HBV DNA by up to 6.86 log in HBeAg-positive, naive patients and by 5.2 log in HBeAg-negative patients or those with lamivudine resistance
            (c) Dose: 0.5 mg orally once daily for patients older than 16 years and nucleoside naive; 1 mg orally once daily for patients older than 16 years with HBV viremia while receiving lamivudine or in lamivudine-resistant HBV
            (d) Dose adjustments required for renal impairment
            (e) Toxicity: Similar to lamivudine with headache, cough, upper respiratory infection, abdominal pain; possibly fewer ALT flares. Rare lactic acidosis. Resistance reported as similar to 1% at 5 years.

v. Tenofovir (Viread 300 mg, Vemlidy 25 mg)
   (a) Nucleotide analog, formulated as tenofovir disoproxil fumarate (Viread) or tenofovir alafenamide (Vemlidy), indicated for chronic HBV infection
   (b) Effective for lamivudine-resistant HBV
   (c) Dose adjustments of tenofovor disoproxil fumarate required for renal impairment. Tenofovir alafenamide is not recommended in patients with CrCl less than 15 mL/min, and for patients on hemodialysis, it should be dosed after dialysis.
   (d) Toxicity: Overall, well tolerated; headache, nausea, and nasopharyngitis most commonly reported; potential renal toxicity, so periodic monitoring of SCr recommended; potential ALT flares on withdrawal; rare lactic acidosis. Tenofovir alafenamide is associated with less renal and bone toxicity.

b. Pegylated interferon
   i. Cytokine with antiviral, antiproliferative, and immunomodulatory effects
   ii. Best predictors of response to treatment are high pretreatment ALT, low-serum HBV DNA, presence of active inflammation on biopsy, and acquisition of infection; adult HBeAg-negative disease responds less favorably to interferon.
   iii. Dosing
      (a) Pegylated interferon is recommended over interferon alfa because of its reduced dosing frequency and improved tolerance.
      (b) Pegylated-α-2a (Pegasys): 180 mcg subcutaneously once weekly for 48 weeks (duration is the same for HBeAg-negative and HBeAg-positive disease)
   iv. If a response is obtained, it is usually long lasting (more than 4 years).
   vi. Treatment with interferon typically results in an increase in ALT 4–8 weeks into treatment. This response is expected; it should not be viewed as an adverse effect of therapy.
   vii. Adverse effects
      (a) Interferon is associated with many serious adverse effects, including bone marrow suppression.
         (1) Leukopenia: May use filgrastim (granulocyte colony-stimulating factor) for support. Requires frequent monitoring of complete blood cell count (every 1–3 months)
         (2) Thrombocytopenia: Minimal data with oprelvekin (interleukin-11). Not used because of many adverse effects including pulmonary hypertension
      (b) Predisposition to infections
      (c) CNS: depression, psychosis, anxiety, insomnia, seizures. Adverse CNS effects occur in 22%–31% of patients.
      (d) Flulike symptoms (tolerance usually develops after a few weeks)
      (e) Anorexia, alopecia, thyroid dysfunction, neuropathy
      (f) Exacerbation of underlying autoimmune disorders (i.e., thyroid). Thyroid-stimulating hormone testing recommended every 3 months
      (g) Ischemic or hemorrhagic cerebrovascular disorders
      (h) Serious hypersensitivity and rash formation
      (i) Manufacturers give recommendations for dose reductions in patients who develop bone marrow suppression and depression while on therapy.
      (j) Contraindicated in patients with current psychosis, a history of severe depression, neutropenia, thrombocytopenia, symptomatic heart disease, decompensated liver disease, and uncontrolled seizures; also use caution in patients with autoimmune disorders

vi. HBV Treatment is summarized in Table 19

Table 19. Summary of Treatment Recommendations for Chronic HBV Infection in Adults

HBV Population	Preferred Treatment Options	Duration	Comments
HBeAg positive	Entecavir and tenofovir are preferred oral agents; use of the other oral reverse transcriptase inhibitors is possible but not preferred	Minimum of 1 yr	Preferred if contraindications or no response to IFNα
	PEG-IFNα	48 wk	If contraindication or no response, use entecavir and tenofovir
HBeAg negative	Entecavir and tenofovir are preferred oral agents; use of the other oral reverse transcriptase inhibitors is possible but not preferred	> 1 yr	Preferred if contraindications or no response to IFNα
	PEG-IFNα	≥ 1 yr	If contraindication or no response, use entecavir and tenofovir
Development of resistant HBV	Lamivudine, telbivudine, or entecavir resistance: Add or switch to tenofovir Adefovir resistance: Add or switch to entecavir Multidrug resistance: Combined tenofovir and entecavir	N/A	Confirm resistance with genotypic testing; reinforce adherence to therapy

N/A = not applicable; PEG-IFNα = pegylated interferon alfa.

4. Preventive strategies
   a. Vaccination (preexposure); indicated in the following groups:
      i. All infants, children, and adults age 19–59 years
      ii. Adults 60 years and older with hepatitis risk factors including:
         (a) Individuals at risk of infection by sexual exposure (sex partners or live with someone with hepatitis B; sexually active but not in a mutually monogamous relationship; have a sexually transmitted infection; men who have sex with men)
         (b) Individuals at risk of infection by percutaneous or mucosal exposure to blood (injection drug use; occupational risk of exposure to blood or blood-contaminated body fluids; patients receiving hemodialysis; patients with diabetes)
         (c) Others (international travelers to countries where hepatitis B is common; individuals with hepatitis C, chronic liver disease, or HIV infection; incarcerated individuals)

b. Available HBV vaccines (dose schedules vary by age)
   i. Dose schedules (Table 20)

Table 20. Dose Schedules for Hepatitis B Vaccinations

Vaccine[a]	Intramuscular Dose[b]	Schedule
Heplisav-B	≥ 18 yr: 0.5 mL	Two doses (0 and 1 mo)
Engerix-B	Birth – 19 yr: 0.5 mL ≥ 20 yr: 1 mL	Three doses (0, 1, and 6 mo)
	Adults receiving hemodialysis: 2 mL	Four doses (0, 1, 2, and 6 mo)
PreHevbrio (3-Antigen)	>/= 18 yr: 1 mL	Three doses (0, 1, and 6 mo)
Recombivax HB	Birth – 19 yr: 0.5 mL[c] ≥ 20 yr: 1 mL	Three doses (0, 1, and 6 mo)
	Adults receiving hemodialysis: 1 mL of high-dose formulation (40 mcg)	Three doses (0, 1, and 6 mo)
Twinrix (HAV and HBV)	≥ 18 yr: 1 mL	Three doses (0, 1, and 6 mo)

[a]All listed vaccines should be refrigerated (2°C–8°C). Do not freeze.

[b]All listed vaccines should be administered intramuscularly in the deltoid muscle for adults, adolescents, and children ≥ 1 yr whose deltoid is large enough for intramuscular injection. For children < 1 yr, the anterolateral aspect of the thigh should be used as the intramuscular injection site.

[c]Ages 11–15 alternative dosing schedule: two intramuscular doses of 10 mcg/1 mL at 0 and 4–6 mo.

HAV = hepatitis A virus.

   ii. Obtain titers 1–2 months after the third dose of the series for HCPs.
   iii. HBV vaccines are available as combination products with HAV (Twinrix), DTP/IPV (Pediarix), and Hib (Comvax).

c. Postexposure prophylaxis
   i. Exposure can result in the need for HBV vaccine or immune globulin.
   ii. Doses of HBV immune globulin are 0.06 mL/kg intramuscularly and must be given within 7 days of exposure.
   iii. Patient populations requiring postexposure prophylaxis
      (a) Perinatal transmission
         (1) Children born to HBsAg-positive mothers should receive the first dose of the three-dose vaccine series plus HBV immune globulin within 12 hours of birth.
         (2) Children born to mothers with unknown HBsAg status (but suspected) should receive the first dose of the three-dose vaccine series within 12 hours of birth; testing should be performed on the child, and if positive, HBV immune globulin should be administered within 1 week.
         (3) Infants weighing less than 2 kg at birth whose mothers are documented as HBsAg negative should receive the first dose of the vaccine series 1 month after birth or at hospital discharge, whichever comes first.
      (b) Sexual contact or household contact with an infected person: Should receive HBV immune globulin plus vaccine series if exposed person is previously unvaccinated
      (c) Sexual contact or household contact with an HBV carrier: Should receive vaccine series if exposed person was previously unvaccinated

(d) Postexposure recommendations for HCPs (Table 21)

Table 21. Centers for Disease Control and Prevention Recommendations for Management of HBV Postexposure for HCPs

HBV Status of HCP	Postexposure Testing		Postexposure Prophylaxis		Postvaccination Serologic Testing
	Source Patient (HBsAg)	HCP Testing (anti-HBs)	HBIG	Vaccination	
Documented responder	No action needed				
Documented nonresponder after six doses	Positive or unknown	—	HBIG × 2 separated by 1 mo	—	No
	Negative	No action needed			
Response unknown after one complete series	Positive or unknown	<10 mIU/mL	HBIG × 1	Initiate revaccination	Yes
	Negative	<10 mIU	None		
	Any result	≥10 mIU	No action needed		
Unvaccinated or incompletely vaccinated or vaccine refusers	Positive or unknown	—	HBIG × 1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

HBIG = hepatitis B immune globulin; HCP = health care provider.

D. HCV
1. Background
   a. RNA virus: six genotypes (50 subtypes)
      i. Genotype 1 (subtypes 1a and 1b) accounts for 70%–75% of infections in the United States.
      ii. Genotypes 2 (subtypes 2a, 2b, and 2c) and 3 (3a and 3b) are less common in the United States.
      iii. Genotype helps determine therapy duration and likelihood of responding to therapy.
   b. Leading cause of liver disease and liver transplantation in the United States; also a common cause of hepatocellular carcinoma
   c. Viral replication occurs in the hepatocyte (virus is not directly cytopathic).
   d. Transmission is mainly bloodborne (transfusion, intravenous drug abuse). HCV risk factors include:
      i. HIV infection
      ii. Current or former injection drug use (including historical and one-time use)
      iii. Patients who ever received maintenance hemodialysis
      iv. Prior recipients of transfusions or organ transplants (received clotting factor concentrates produced before 1987, received a transfusion of blood or blood components before July 1992, received an organ transplant before July 1992, or notified that they received blood from a donor who later tested positive for HCV infection)
      v. Health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposures to HCV-positive blood
      vi. Children born to mothers with HCV infection
   e. Associated with acute and chronic infection; after acute infection, most patients (60%–85%) develop chronic infection
2. Clinical features: About 30% of patients are asymptomatic.
   a. Acute infection: Symptoms present 4–12 weeks after exposure; most patients are asymptomatic and seldom progress to fulminant disease; those who develop symptoms have nonspecific findings such as malaise, weakness, anorexia, and jaundice.

b. *Chronic infection* is defined as the presence of viral RNA in the serum for 6 months or more.
    i. It may be associated with the long-term development of end-stage liver disease, cirrhosis, hepatocellular carcinoma.
    ii. Progression to complications and end-stage liver disease can be accelerated by concurrent alcohol use and coinfection with HIV; younger female patients have slower progression.
c. Extrahepatic manifestations: rheumatoid symptoms, glomerulonephritis, cryoglobulinemia

3. Diagnosis and monitoring
    a. Clinical signs and symptoms include nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Many patients have asymptomatic disease.
    b. Once in a lifetime HCV testing is recommended for all individuals aged 18 years or older and for pregnant women with each pregnancy.
    c. In addition, one-time HCV testing for patients with HCV risk factors, including:
        i. People with HIV
        ii. People who ever injected drugs and shared needles, syringes, or other drug preparation equipment, including those who injected once or a few times many years ago
        iii. People with select medical conditions, including those who ever received maintenance hemodialysis or those with persistently abnormal ALT levels
        iv. Prior recipients of transfusions or organ transplants, including clotting factor concentrates produced before 1987 or transfusion of blood or blood components or organ transplant before July 1992, or those notified that they received blood from a donor who later tested positive for HCV
        v. Health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposures to HCV-positive blood
        vi. Children born to mothers with HCV infection
        vii. Routine periodic testing for people with ongoing risk factors, including current injection drug users or those who ever received maintenance hemodialysis
    d. Laboratory
        i. Serum anti-HCV antibodies (99% sensitivity and specificity [enzyme immunoassays]) are used as an initial screening for HCV. The presence of anti-HCV antibody does not confer protective immunity from subsequent infection.
            (a) If serum anti-HCV antibodies are positive, confirmatory testing by a sensitive HCV RNA test is warranted.
            (b) Quantitative HCV RNA testing to document baseline viremia before initiating antiviral therapy
            (c) Sustained virologic response (SVR) is undetectable HCV RNA 12 weeks after completion of treatment; it is considered a virologic cure.
        iii. Liver biopsy, imaging, or noninvasive markers to evaluate liver fibrosis is recommended.
        iv. Genotyping: Genotype 1 is the most common genotype in the United States. Genotypes 2 and 3 are the other two most common genotypes in the United States.

4. Treatment
    a. Acute HCV infection
        i. Preexposure or postexposure prophylaxis is not recommended.
        ii. The same regimens used for chronic HCV are recommended for treatment.
    b. Chronic infection
        i. Therapy goal is to attain a SVR, defined as the absence of detectable HCV RNA 12 weeks after treatment. Obtaining undetectable concentrations at 12 weeks is considered a clinical cure.
        ii. With the availability of direct-acting antivirals (DAAs) therapies, treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be altered by treating HCV, transplantation, or other directed therapy.

iii. DAAs carry a risk of reactivation of HBV infection. Patients receiving DAA therapy should be tested and monitored for HBV reactivation.

c. Ribavirin in the treatment of HCV infection
   i. Oral nucleoside analog
   ii. Available as 200-mg tablets (Copegus) or capsules (Rebetol, Ribasphere; generic available)
   iii. Weight-based dosing of ribavirin, administered daily in two divided doses: for patients weighing less than 66 kg: 800 mg daily; 66–80 kg: 1000 mg daily; 81–105 kg: 1200 mg daily; greater than 105 kg: 1400 mg/day. Reduced dosing may be considered in patients with decompensated cirrhosis.
   iv. Significant adverse effect profile
      (a) Hemolytic anemia can occur in up to 10% of patients (usually within 1–2 weeks of initiating therapy); may worsen underlying cardiac disease; monitor complete blood cell count (CBC) at baseline, 2 weeks, 4 weeks, and periodically thereafter. In patients with no cardiac history, decrease the dose to 600 mg/day if hemoglobin drops to 10 g/dL or less, and discontinue when hemoglobin drops to 8.5 g/dL or less. In patients with a cardiac history, decrease the dose to 600 mg/day if hemoglobin drops more than 2 g/dL in any 4-week period during treatment. Discontinue if hemoglobin drops to less than 12 g/dL 4 weeks after dose reduction. Epoetin or darbepoetin can be used to stimulate red blood cell production, improve anemia, and sustain initial starting dose. It is also necessary to confirm that iron study results are normal and within range during treatment.
      (b) Teratogenicity: category X drug; requires a negative pregnancy test at baseline and every month up to 6 months after treatment, as well as the use of two forms of barrier contraception during treatment and for 6 months after treatment; applies to women taking the drug and female partners of male patients taking ribavirin
      (c) Other possible adverse events include pancreatitis, pulmonary dysfunction (dyspnea, pulmonary infiltrate, and pneumonitis), insomnia, irritability or depression (often called "riba rage"), and pruritus.

d. NS5B/A polymerase inhibitors sofosbuvir (Sovaldi) and sofosbuvir/ledipasvir (Harvoni)
   i. Indications
      (a) Sofosbuvir: HCV genotypes 1–6, including those with hepatocellular carcinoma meeting Milan criteria and those with HCV/HIV coinfections
      (b) Sofosbuvir/ledipasvir: genotype 1, 4, 5, or 6 infection
   ii. Dosing: 400-mg tablet once daily with or without food
   iii. Adverse effects: fatigue, headache
   iv. Drug interactions
      (a) Avoid use with potent P-glycoprotein (P-gp) inducers.
      (b) Concentrations are significantly affected by anticonvulsants (carbamazepine, phenytoin, phenobarbital, and oxcarbazepine), rifabutin, rifampin, St. John's wort, and tipranavir/ritonavir.
      (c) Avoid using with amiodarone because of symptomatic bradycardia. The mechanism of this interaction is not known.
      (d) Coadministration with acid-suppressive therapy may reduce DAA concentrations and is not recommended.
      (e) Coadministration with an HMG-CoA inhibitor may increase HMG-CoA inhibotor systemic concentrations and increase the risk of statin-related adverse effect. Coadministration is not recommended.

e. NS5A/B inhibitor combination velpatasvir / sofosbuvir (Epclusa)
   i. Indication: Genotype 1–6 infection
   ii. Dosing: velpatasvir 100 mg / sofosbuvir 400 mg fixed-dose combination tablet once daily for 12 weeks. Weight-based ribavirin is added if decompensated cirrhosis is present with HCV genotypes 1–6.
   iii. Adverse effects: headache and fatigue
   iv. Drug interactions
      (a) Contraindicated with inducers of P-gp and moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine), which can decrease plasma concentrations of sofosbuvir and/or velpatasvir.
      (b) Avoid use of amiodarone and sofosbuvir because of symptomatic bradycardia.
      (c) Coadministration with acid-suppressive therapy may reduce DAA concentrations and is not recommended.
      (d) Coadministration with an HMG-CoA inhibitor may increase HMG-CoA inhibotor systemic concentrations and increase the risk of statin-related adverse effect. Coadministration is not recommended.

f. NS3/4A and NS5A inhibitor combination glecaprevir and pibrentasvir (Mavyret)
   i. Indications
      (a) Genotype 1–6 infection with or without compensated cirrhosis (Child-Turcotte-Pugh A)
      (b) Recommended as an option for treatment-experienced patients depending on prior DAA treatment regimen.
   ii. Dosing: glecaprevir 100 mg / pibrentasvir 40mg fixed dose combination tablet, three tablets once daily with food for:
      (a) Eight weeks for genotype 1–6 treatment-naive patients without cirrhosis or compensated cirrhosis (except those with compensated cirrhosis who are coinfected with HIV).
      (b) 16 weeks for patients previously treated, depending on prior regimen
   iii. Adverse effects: headache, fatigue, nausea. NS3/4A protease inhibitors are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.
   iv. Drug interactions:
      (a) Avoid use with P-gp or CYP3A inducers, because this can reduce the concentration of glecaprevir and pibrentasvir (carbamazepine, efavirnez, St. John's wort). It is contraindicated with atazanavir or rifampin.
      (b) Coadministration with acid-suppressive therapy may reduce DAA concentrations and is not recommended.
      (c) Coadministration with an HMG-CoA inhibitor may increase HMG-CoA inhibotor systemic concentrations and increase the risk of statin-related adverse effect. Coadministration is not recommended.

g. NS3/4A inhibitor Grazoprevir combined with NS5A inhibitor elbasvir (Zepatier)
   i. Indication: Geonotypes 1 or 4 infection with or without ribavirin
   ii. Dosing: Grazoprevir 100 mg / elbasvir 50 mg fixed-dose combination tablet once daily for 12 or 16 weeks.
      (a) Testing for NS5A resistance-associated substitutions (RASs) is recommended. If RASs are present, another recommended regimen should be used.
   iii. Adverse effects
      (a) ALT elevations: Check ALT at baseline, 8 weeks of therapy, and 12 weeks of therapy if 16 week duration is indicated (contraindicated in Child-Pugh class B or C).

(b) Headache, fatigue
(c) NS3/4A protease inhibitors are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.

iv. Drug interactions
(a) Contraindicated in combination with OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz.
(b) Coadministration with acid-suppressive therapy may reduce DAA concentrations and is not recommended.
(c) Coadministration with an HMG-CoA inhibitor may increase HMG-CoA inhibotor systemic concentrations and increase the risk of statin-related adverse effect. Coadministration is not recommended.

h. NS5A/B and NS3/4A inhibitor combination velpatasvir, sofosbuvir, and voxilaprevir (Vosevi)
i. Indications
(a) Genotypes 1–6 infection with or without compensated cirrhosis (Child-Turcotte-Pugh A) in patients who have been treated with an HCV regimen containing an NS5A inhibitor.
(b) Recommended as an option for treatment-experienced patients depending on prior DAA treatment regimen.

ii. Dosing: sofosbuvir 400 mg / velpatasvir 100 mg / voxilaprevir 100 mg fixed dose combination tablet once daily with food for 12 weeks
iii. Adverse effects: headache, fatigue, diarrhea, nausea. NS3/4A protease inhibitors are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.
iv. Drug interactions: See velpatasvir / sofosbuvir (Epclusa) listing above.

i. Effective and simplified treatment regimens are recommended in an effort to increase the number of health care providers who are able to prescribe curative HCV treatment and to increase the number of patients who are effectively treated for HCV. Simplified treatment regimens are not appropriate for patients who have received prior HCV treatment, have concurrent HIV or are HBsAg positive, are pregnant, have cirrhosis, prior liver transplant, or known or suspected hepatocellular carcinoma. Treatment recommendations for chronic HCV infection in treatment-naive adults are included in Table 22.

Table 22. Simplified Treatment Algorithm for Treatment-Naive Adult Patients with HCV (irrespective of genotype unless noted)

Patients without Cirrhosis	Patients with Compensated Cirrhosis (Child-Pugh-Turcotte class A)
Glecaprevir (300 mg)/pibrentasvir (120 mg) daily with food × 8 wk	Glecaprevir (300 mg)/pibrentasvir (120 mg) daily with food × 8 wk
Sofosbuvir (400 mg)/velpatasvir (100 mg) daily × 12 wk	Sofosbuvir (400 mg)/velpatasvir (100 mg) daily × 12 wk for genotypes 1, 2, 4, 5, or 6. Genotype 3 requires baseline NS5A RAS testing. Sofosbuvir/velpatasvir can be used if Y93H is absent

HCV = hepatitis C virus; RAS = resistance-associated substitution.

j. Table 23 includes HCV genotype specific treatment recommendations.

Table 23. Recommended Treatment Regimens for Chronic HCV Infection in Treatment-Naive Patients With or Without Compensated Cirrhosis by HCV Genotype[a]

Genotype	Without Cirrhosis	With Compensated Cirrhosis
1a	GLE (300 mg)/PIB (120 mg) for 8 wk LDV (90 mg)/SOF (400 mg) for 12 wk[b] VEL (100 mg)/SOF (400 mg) for 12 wk	GLE (300 mg)/PIB (120 mg) for 8 wk LDV (90 mg)/SOF (400 mg) for 12 wk VEL (100 mg)/SOF (400 mg) for 12 wk
1b	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk EBR (50 mg)/GZR (100 mg) for 12 wk[c] LDV (90 mg)/SOF (400 mg) for 12 wk[b]	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk EBR (50 mg)/GZR (100 mg) for 12 wk LDV (90 mg)/SOF (400 mg) for 12 wk
2	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk
3	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk[d]
4	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk EBR (50 mg)/GZR (100 mg) for 12 wk LDV (90 mg)/SOF (400 mg) for 12 wk[e]	GLE (300 mg)/PIB (120 mg) for 8 wk[f] VEL (100 mg)/SOF (400 mg) for 12 wk EBR (50 mg)/GZR (100 mg) for 12 wk LDV (90 mg)/SOF (400 mg) for 12 wk
5 or 6	GLE (300 mg)/PIB (120 mg) for 8 wk VEL (100 mg)/SOF (400 mg) for 12 wk LDV (90 mg)/SOF (400 mg) for 12 wk[g]	(Same recommendations for genotype 5 or 6 with or without compensated cirrhosis)

[a]See guidelines for treatment recommendations after failure of Pegylated interferon therapy or direct-acting antivirals.

[b]For patients who are uninfected with HIV, and whose HCV RNA less than 6 million IU/mL, can use 8 week duration of therapy.

[c]Consider 8-week regimen if mild fibrosis.

[d]Only recommended in patients without baseline NS5A Resistance Associated Substitutions (RAS) Y93H.

[e]Consider 8-week regimen if no cirrhosis, HCV RNA less than 6 million IU/mL, and absence of genotype 4r.

[f]For patients co-infected with HIV, 12-week duration is recommended.

[g]Not recommended for genotype 6e if subtype is known.

EBR = elbasvir; GLE = glecaprevir; GZR = grazoprevir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV = ledipasvir; PIB = pibrentasvir; SOF = sofosbuvir; VEL = velpatasvir.

See treatment guidelines for alternative recommendations.

5. Monitoring
    a. Baseline HCV RNA, genotype, quantitative HCV RNA (HCV viral load), CBC, liver function tests (LFTs), and calculated GFR. HIV and hepatitis B surface antigen testing. Pregnancy test for women. Evaluate for potential drug-drug interactions.
    b. On therapy: Medication adherence, potential drug-drug interactions.
    c. After treatment: Check HCV RNA at 12 weeks to assess for SVR.
6. Prevention of HCV
    a. No vaccine or immune globulin available
    b. Risk factor modification
        i. Intravenous drug abuse: Methadone maintenance, syringe exchange
        ii. Sexual contact: Appropriate barrier contraception
        iii. Avoid blood exposure: Occupational (universal precautions) or other contact (e.g., sharing toothbrushes or razors or receiving a tattoo)
        iv. The HAV and HBV vaccine to prevent further progression of liver disease

Patient Cases

8. A 45-year-old woman (height 63 inches, weight 54 kg) with a history of intravenous drug abuse is evaluated in the clinic for chronic HBV infection. Although she received the HBV diagnosis 8 months ago, she has not been treated for it. Laboratory values today include HBsAg positive, HBeAg positive, AST 650 IU/mL, ALT 850 IU/mL, HBV DNA 107,000 IU/mL, SCr 1.9 mg/dL, INR 1.3, and albumin 3.9 g/dL. She has no evidence of ascites or encephalopathy. A liver biopsy reveals severe necroinflammation and bridging fibrosis. Resistance testing reveals the YMDD mutation. Which is the best course of action?
   A. Withhold drug therapy and recheck HBV DNA in 6 months.
   B. Initiate entecavir 0.5 mg/day.
   C. Initiate lamivudine 100 mg/day.
   D. Initiate tenofovir disoproxil fumarate 300 mg/day.

9. A 38-year-old white man (height 72 inches, weight 75 kg) is seen today for a new diagnosis of chronic HCV, genotype 1a. Pretreatment laboratory values include AST 350 IU/mL, ALT 420 IU/mL, HCV RNA 950,000 IU/mL, SCr 1 mg/dL, hemoglobin 12 g/dL, and WBC 12 × 10^3 cells/mm^3. A liver biopsy reveals fibrosis without cirrhosis. He reports no known drug allergies. Which option is best for treating this patient's chronic HCV infection?
   A. Withhold therapy and reassess in 12 months.
   B. Initiate glecaprevir and pibrentasvir for 8 weeks.
   C. Initiate sofosbuvir and ledipasvir for 8 weeks.
   D. Initiate pegylated interferon, ribavirin, and sofosbuvir for 16 weeks.

VII. NAUSEA AND VOMITING

- A. Definitions and Pathophysiology
  - 1. Definitions
    - a. Nausea: Unpleasant sensation of the imminent need to vomit; may or may not lead to vomiting
    - b. Vomiting: Forceful expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature
  - 2. Pathophysiology
    - a. Stimuli for vomiting are processed through several major anatomic areas, each of which has various receptors associated with input to the medullary vomiting center.
      - i. Visceral stimuli: Mediated through dopamine and serotonin receptors. Major stimuli include:
        - (a) Gastric irritants
        - (b) Nongastric stimuli (peritonitis, intestinal or biliary distension, pancreatitis, gastroparesis)
        - (c) Abdominal radiation
        - (d) Chemotherapeutic agents
        - (e) Pharyngeal stimulation

ii. Chemoreceptor trigger zone (located in the area postrema): Mediated by dopamine (D_2), serotonin, and some histamine (H_1) and muscarinic (M_1) and substance P/neurokinin 1; major stimuli include:
   (a) Medications: Opiates, dopamine agonists, digoxin, chemotherapeutic agents, macrolides, general anesthetics
   (b) Metabolic disturbances (uremia, diabetic ketoacidosis, hypercalcemia, hypoxemia)
   (c) Bacterial toxins
   (d) Radiation therapy
iii. Vestibular labyrinths: Mediated through H_1 and M_1. Major stimuli include:
   (a) Motion sickness
   (b) Labyrinth infection
iv. Cerebral cortex: Receptor involvement not well characterized; noxious odors, visions, and tastes

Table 24. Common Clinical Conditions Associated with Nausea and Vomiting

Category	Conditions
Infectious	Viral or bacterial gastritis or gastroenteritis, pyelonephritis
Gastrointestinal	Pancreatitis, gastroparesis, hepatitis, gastroesophageal reflux disease
Central nervous system	Migraine, stroke, pain, seizures, motion sickness, meningitis
Endocrine or metabolic	Pregnancy, uremia, diabetic ketoacidosis, hypercalcemia
Cardiovascular	Myocardial infarction, heart failure
Other	Postoperative, cerebral mass

b. Clinical consequences of nausea and vomiting include dehydration, electrolyte disturbances, aspiration, and Mallory-Weiss syndrome.

B. Treatment and prevention strategies
1. Remove or treat the underlying cause (Table 24)
2. Correct dehydration and electrolyte disturbances. Oral rehydration is preferred, if possible, with oral rehydration solutions (e.g., Pedialyte, diluted Gatorade).
3. Drug treatment: Use drugs that target receptors involved with stimuli. May need combination of drugs with different mechanisms. Also may need alternative dose forms (intravenous, subcutaneous, suppository).
   a. Major drug classes of antiemetics: All are antagonists at the respective receptors. (Table 25)
   b. Drugs of choice for different situations include:
      i. General medical use: phenothiazines, serotonin antagonists
      ii. Chemotherapy induced: serotonin antagonists, NK1 antagonists, corticosteroids, and olanzapine as adjunctive therapy (See "Oncology Supportive Care" chapter for treatment and prevention.)
      iii. Postoperative: serotonin antagonists, scopolamine, corticosteroids
      iv. Motion sickness: antihistamines, scopolamine
      v. Pregnancy: phosphorylated carbohydrate solution, pyridoxine, antihistamines, ginger
      vi. Gastroparesis: metoclopramide

Table 25. Select Antiemetics

Drug	Formulations	Comments
Phenothiazines		
Promethazine (Phenergan)	Tablet, suppository, injection	Antidopaminergic, anticholinergic, and antihistaminergic activity; can cause EPS, injection-site irritation (do not use subcutaneously), sedation IV formulation should be diluted (risk of tissue necrosis)
Prochlorperazine (Compazine)	Tablet, syrup, suppository, injection	Mainly antidopaminergic activity; can cause EPS, injection-site irritation (do not use subcutaneously)
Serotonin antagonists		
Ondansetron (Zofran)	Tablet, ODT, oral solution, injection, oral-soluble film (Zuplenz)	Overall, well tolerated; no liquid required for ODT or soluble film; contraindicated with apomorphine; associated with QTc prolongation; correct hypomagnesemia and hypokalemia
Granisetron (Kytril, Sancuso, Sustol)	Injection, tablet, oral solution, patch	Overall, well tolerated; associated with QTc prolongation
Palonosetron (Aloxi)	Injection	Long duration of action is 24 hr to 5 days; only one dose required
Antihistamines		
Dimenhydrinate (Dramamine), cyclizine (Marezine), meclizine (Bonine), doxylamine (Unisom)	Tablet, oral liquid, injection	Take 30–60 min before travel; risk of sedation and anticholinergic adverse effects
Butyrophenones		
Haloperidol, droperidol	Injection, tablet	Risk of extrapyramidal adverse effects; risk of QTc prolongation; requirement for baseline ECG and 2- to 3-hr postdose cardiac monitoring with the use of injectable agents
Corticosteroids		
Dexamethasone (Decadron)	Injecton, tablet, oral solution	Short-term use to prevent postoperative nausea and vomiting or chemotherapy-induced nausea and vomiting
Neurokinin 1 antagonists		
Aprepitant, fosaprepitant (Emend)	Capsule, injection	Targets substance P/neurokinin 1 (NK1) receptors; reduces efficacy of warfarin and oral contraceptives; dose-dependent inhibitor of CYP3A4
Netupitant / palonosetron (Akynzeo)	Capsule	Targets substance P/neurokinin 1 (NK1) receptors and 5-HT3; avoid in severe renal or hepatic disease, drug-drug interactions by CYP enzymes
Rolapitant (Varubi)	Tablet	Targets neurokinin 1 (NK1) receptors; long half-life (7 days)
Miscellaneous agents		
Scopolamine (Transderm Scop)	Patch	Apply topically (often behind the ear) 4 hr before travel; can wear for up to 72 hr; do not cut patch; risk of anticholinergic adverse effects
Dronabinol (Marinol), nabilone (Cesamet)	Capsule	Delta-9 tetrahydrocannabinol; targets central endogenous cannabinoid receptors; used most often for chemotherapy-induced N/V; can cause appetite stimulation, euphoria, cognitive impairment
Phosphorylated carbohydrate solution (Emetrol)	Oral solution	Use undiluted for best effect; do not use >1 hr (or maximum of five doses); safe in pregnancy; avoid in diabetes and fructose intolerance
Doxylamine/ pyridoxine (Diclegis, Bonjesta)	Delayed-release tablet (10 mg/10 mg)	Prescription product approved for NVP in women who do not respond to conservative management; OTC doxylamine and pyridoxine may be considered; pregnancy category A

CYP = cytochrome P450; ECG = electrocardiogram; EPS = extrapyramidal symptoms; N/V = nausea and vomiting; NVP = nausea and vomiting of pregnancy; ODT = orally disintegrating tablet; SR = sustained release.

c. Nondrug therapy for nausea and vomiting: acupressure and acustimulation wristbands (Sea-Band, Reliefband); work by stimulating the pericardium 6 (P6) point.

VIII. PANCREATITIS

A. Classification and pathophysiology
   1. Acute
      a. Characterized by inflammation in the pancreas ranging from mild to severe
      b. An initial insult leads to the release of trypsin in the pancreas, leading to the activation of pancreatic enzymes and intrapancreatic inflammation and complications. It can then progress to extrapancreatic complications. It is usually reversible once the underlying cause is addressed.
      c. Two distinct phases
         i. Early (within 1 week): associated with systemic inflammatory response syndrome or organ damage
         ii. Late (more than 1 week): associated with local complications
      d. Typical signs and symptoms include abdominal pain and distension, nausea, vomiting, jaundice, and fever.
         i. Local complication: necrosis, hemorrhage, pseudocyst, abscess, infection
         ii. Systemic complications: systemic inflammatory response syndrome, acute respiratory distress syndrome, shock, organ failure
      e. Main causes of acute pancreatitis
         i. Long-term alcohol abuse
         ii. Gallstones
         iii. Drugs (Box 5)

Box 5. Common Causes of Drug-Induced Pancreatitis

Amiodarone
Asparaginase
Azathioprine/mercaptopurine
Cannabis
Didanosine
Diuretics (furosemide, hydrochlorothiazide)
Estrogens
Exenatide
Mesalamine/sulfasalazine
Pentamidine
Sitagliptin
Tetracycline
Trimethoprim/sulfamethoxazole
Valproic acid

         iv. Post–endoscopic retrograde cholangiopancreatography
         v. Hypertriglyceridemia (generally greater than 1000 mg/dL)
         vi. Idiopathic
         vii. Structural abnormalities
         viii. Toxins (scorpion venom)
         ix. Trauma
         x. Ischemia

2. Chronic
    a. Characterized by irreversible structural and functional loss of pancreatic function caused by long-standing inflammation and repeated injury
    b. Repeated injury results in loss of both exocrine and endocrine function.
    c. Typical signs and symptoms include chronic abdominal pain, steatorrhea, weight loss or cachexia, jaundice, and hyperglycemia. Complications include diabetes, pseudocysts, calcification, ascites, and biliary stricture.
    d. Risk factors for chronic pancreatitis are based on the M-ANNHEIM classification. The M-ANNHEIM classification system is an objective, relatively noninvasive approach to categorizing patients with acute or chronic pancreatitis on the basis of their disease etiology, clinical stage, and disease severity.
    M = Multiple risk factors
    A = Alcohol consumption
    N = Nicotine
    N = Nutritional factors (high fat and protein, hyperlipidemia)
    H = Hereditary factors
    E = Efferent duct factors
    I = Immunologic factors
    M = Miscellaneous and rare factors (includes drugs)

B. Diagnosis
    1. Acute pancreatitis
        a. Diagnosis is typically based on two of the three following criteria:
            i. Presence of abdominal pain
            ii. Laboratory diagnosis: Serum lipase (greater than 3 times the ULN) is the most sensitive test. Patients may also have hyperglycemia and other electrolyte abnormalities related to vomiting. Patients often have a leukocytosis and a fever.
            iii. Imaging: Abdominal ultrasonography and computed tomography (CT) scan to evaluate pancreas, biliary system, and presence of local complications
        b. Severity and prognosis (Table 26)

Table 26. Common Scoring Systems to Classify Severity and Prognosis of Acute Pancreatitis

Atlanta Symposium Criteria for Acute Pancreatitis	Ranson Criteria for Prognosis[a]	
Mild: absence of organ failure or local complications Moderately severe: local complications or transient organ failure (< 48 hr) Severe: persistent organ failure > 48 hr	At admission: Age > 55 yr (>70 yr) WBC >16,000/L (18,000/L) Blood glucose > 200 mg/dL (220 mg/dL) Serum lactate dehydrogenase > 350 IU/L (>400 IU/L) Serum AST > 250 IU/L (same)	Within next 48 hr: Decrease in hematocrit by > 10% (same) Estimated fluid sequestration of > 6 L (4 L) Serum calcium < 8 mg/dL (same) Pao_2 < 60 mm Hg (omitted) BUN concentration increase > 5 mg/dL after IV fluid hydration (> 2 mg/dL) Base deficit of > 4 mmol/L (6 mmol/L)

[a]Values in parentheses are for gallstone induced; meeting more than three criteria indicates severe disease.

AST = aspartate transaminase; BUN = blood urea nitrogen; WBC = white blood cell count.

2. Chronic pancreatitis: Diagnosis is typically based on the clinical signs and symptoms plus laboratory and imaging.
    a. Laboratory diagnosis: Serum lipase may be normal; hyperglycemia and low albumin or prealbumin may also be present.
    b. Imaging: CT scan may reveal pancreatic calcification or pseudocyst.

C. Treatment strategies
1. Acute pancreatitis: Treatment is largely supportive; should include removal or treatment of underlying cause if possible.
    a. Temporarily withhold oral intake and provide rehydration with intravenous fluids, typically 250–500 mL/hour of lactated Ringer or normal saline solution. American Gastroenterological Association offers a recommendation for goal-directed intravenous fluids titrated to maintain heart rate; mean arterial pressure; central venous pressure; urine output; blood, urea, and nitrogen concentration; and hematocrit (Conditional recommendation / very low quality evidence). Treat electrolyte disturbances (hypokalemia, hypocalcemia, hyperglycemia).
    b. Pain management involves the use of intravenous narcotics (avoid meperidine). Patient-controlled analgesia is often used.
    c. Antiemetics: Intravenous ondansetron, prochlorperazine, or promethazine
    d. Nutrition: If pancreatitis is mild, then early (less than 24 hours) oral feeding can be resumed if no vomiting is present. If severe pancreatitis is present, use enteral nutrition to prevent infectious complications. Avoid total parenteral nutrition (higher rates of infection, mortality, and length of stay).
    e. Antibiotics, in general, are not recommended for routine prophylaxis in severe pancreatitis. Antibiotics can be used if extrapancreatic infection is present. If infected necrosis is present, then carbapenems, fluoroquinolones, or metronidazole may be useful in delaying the need for intervention.
    f. Endoscopic retrograde cholangiopancreatography may be needed for cholangitis or gallstone pancreatitis. This is often followed by cholecystectomy to prevent future episodes.
2. Chronic pancreatitis: Treatment is largely symptomatic.
    a. Abstinence from alcohol is essential. Pharmacologic intervention and supportive care (e.g., Alcoholics Anonymous) may be needed. Smoking cessation is also recommended by the ACG guidelines (strong recommendation, very low-quality evidence).
    b. Antioxidant therapy can be considered to treat pain with chronic pancreatitis. The antioxidants used in clinical trials vary in type and dosage but commonly include selenium, ascorbic acid, beta-carotene, and methionine (conditional recommendation, moderate-quality of evidence).
    c. Pain management often requires a combination of nonnarcotic and narcotic analgesics (long-acting morphine, oxycodone, or transdermal fentanyl) in combination with pancreatic enzyme replacement. Avoid acetaminophen if long-term alcohol use is a factor. Consider adjunctive medications such as pregabalin or selective serotonin reuptake inhibitors (SSRIs) in patients who tolerate oral medications to minimize opioid needs.
    d. Antiemetics: Oral ondansetron, prochlorperazine, or promethazine as needed
    e. Nutrition: Goal is to maximize caloric intake and weight gain and reduce steatorrhea. May need more frequent, lower-fat meals and fat-soluble vitamin supplementation. Long-term enteral or parenteral nutrition may be required.
3. Pancreatic enzyme replacement therapy
    a. Simulate the digestion of food that normally occurs with normal pancreatic enzyme release to reduce maldigestion and malabsorption. Pancreatic enzyme replacement therapy is recommended if the patient experiences weight loss, malnutrition, diarrhea, steatorrhea, osteoporosis, or osteopenia (conditional recommendation, low level of evidence).

b. Products are enteric-coated microspheres or microtablets that contain lipase, amylase, and protease. Meant to mix with food, they release enzymes at intestinal pH values greater than 5.5. Products should not be crushed or chewed.
c. Enzyme products were historically considered nutritional supplements. The FDA has now mandated FDA approval of all enzyme products. (Table 27)

Table 27. Selected Pancreatic Enzyme Replacement Products

Brand Name	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Viokace	10,440 20,880	39,150 78,300	39,150 78,300	Immediate-release tablet; must be administered in combination with a proton pump inhibitor
Creon	3000 6000 12,000 24,000 36,000	15,000 30,000 60,000 120,000 180,000	9500 19,000 38,000 76,000 114,000	Capsules with enteric-coated microspheres (0.17–1.6 mm)
Zenpep	3000 5000 10,000 15,000 20,000 25,000 40,000	14,000 24,000 42,000 63,000 84,000 105,000 168,000	10,000 17,000 32,000 47,000 63,000 79,000 126,000	Capsules with enteric-coated beads (1.8–1.9 mm for 3000/5000 units; 2.2–2.5 mm for all other strengths)
Pancreaze	2600 4200 10,500 16,800 21,000 37,000	15,200 24,600 61,500 98,400 83,900 149,900	8800 14,200 35,500 56,800 54,700 97,300	Capsules with enteric-coated microtablets (2 mm)
Pertzye	4000 8000 16,000 24,000	15,125 30,250 60,500 90,750	14,375 28,750 57,500 86,250	Capsules with bicarbonate-buffered enteric-coated microspheres (0.8–2 mm)

d. Dosing is based on the lipase content (units) of the product.
   i. Starting adult doses are generally 40,000–50,000 units per meal, with a half dose for snacks. May also use weight-based dosing of 500–1000 units/kg per meal for those older than 4 years.
   ii. Maximum dose is 2500 units/kg per dose, 10,000 units/kg/day, or 90,000 units per meal.
   iii. Give enzymes with meals as opposed to before or after meals.
   iv. Titrate according to weight gain and reduction in steatorrhea.
   v. May need to add PPI if maximal response is not seen.

e. Adverse effects of pancreatic enzyme therapy
   i. Nausea or abdominal cramping
   ii. Enzymes are derived from porcine pancreas; this is contraindicated if a pork allergy is present.
   iii. Hyperuricosuria, hyperuricemia
   iv. Fibrosing colonopathy (generally seen with doses greater than 10,000 units/kg/day)
   v. Pregnancy category C

IX. DIARRHEA

A. Classification and pathophysiology
   1. Clinical definition: Alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency (more than three per day) of stool
      a. *Acute* is generally considered less than 72 hours to 14 days.
      b. *Chronic* is generally considered more than 14–30 days.
   2. Can be classified into several major categories related to underlying cause
      a. Secretory
         i. Secondary to enhanced secretion by intestinal mucosa; often, large, watery volume with loss of electrolytes
         ii. Common causes: Bacterial or viral or bacterial enteritis, gastric hypersecretion, carcinoid, stimulant laxatives, bile acid malabsorption, celiac disease, IBD (mucosal)
      b. Osmotic
         i. Secondary to a hyperosmolar gradient in the intestinal lumen
         ii. Common causes: Osmotic laxatives, carbohydrate malabsorption (lactase deficiency), fat malabsorption (pancreatic insufficiency), short bowel syndrome
      c. Exudative or inflammatory
         i. Secondary to inflammation or infiltration or invasion of the intestinal mucosa
         ii. Common causes: IBD, invasive infection (*C. difficile* toxin, enterotoxigenic *Escherichia coli,* cytomegalovirus, *Shigella* species), ischemic colitis, radiation enterocolitis, neoplasm
      d. Altered motility or motor function
         i. Secondary to autonomic nerve dysfunction
         ii. Common causes: diabetic neuropathy, postvagotomy, hyperthyroidism, IBS, Addison disease
   3. Drug-induced diarrhea can occur by a variety of mechanisms. See Box 6 for a list of medications that commonly cause diarrhea.

Box 6. Common Causes of Drug-Induced Diarrhea

Acarbose or miglitol
Antibiotics
Antineoplastics
Colchicine
Digoxin
Laxatives
Levothyroxine (over-replacement)
Metoclopramide
NSAIDs
Prostaglandins (misoprostol)
Orlistat
Sorbitol (sugar-free products)

B. Diagnosis
   1. Conduct a thorough patient history.
      a. Evaluate for disease- and drug-induced causes (laxative, recent antibiotic use), recent travel history, and temporal relation to food intake.
      b. Assess fluid and electrolyte status.
      c. Assess CBC and stool culture, and evaluate for ova and parasites if infectious cause is suspected. Assess for *C. difficile* toxin and culture if there has been recent antibiotic use or hospitalization.
      d. Evaluate stool pH, electrolytes, osmolarity, or fat content, if indicated.
      e. Imaging (abdominal CT scan) or endoscopy with biopsy may be indicated, particularly for inflammatory diarrhea or suggestion of neoplasm or celiac disease.
   2. Referral to higher level of care or further evaluation may be necessary for some patients.
      a. Immunocompromised
      b. Infants and children
      c. Pregnant women
      d. Presence of fever
      e. Blood in the stool
      f. Weight loss (greater than 5%)
      g. Suspected invasive infection

C. Treatment strategies
   1. Removal or treatment of underlying causes, if possible
   2. Rehydration
      a. Intravenous fluids appropriate for hospitalized patients
      b. Oral rehydration appropriate for all patients if no vomiting is present
         i. Sodium and glucose are key ingredients of oral rehydration solutions, because they have active uptake into the intestinal mucosa even during active diarrhea. This results in water being pulled back into circulation. Other formulations (popsicles) are also available.
         ii. Gatorade may need to be diluted because it has a large amount of carbohydrates.
   3. Dietary modifications
      a. Avoid dairy products because transient lactase deficiency can occur.
      b. "BRAT" diet for adults (mild foods such as bananas, rice, applesauce, toast) is sometimes recommended for short-term use, though definitive supporting data are limited.
      c. May need to interrupt feedings for pediatric patients
   4. Drug therapy for diarrhea is listed in Table 28 (see "Infectious Diseases" chapter for management of infectious causes)

Table 28. Select Therapies for the Management of Diarrhea

Drugs	Mechanism	Role	Adverse Effects and Precautions
Bismuth subsalicylate	Antisecretory, binds toxins	Mild-moderate diarrhea; prevention of traveler's diarrhea	Stool discoloration; avoid in salicylate allergy, age <12 yr, pregnancy, nursing; caution with anticoagulants; can bind other drugs; can interfere with some radiographic procedures
Crofelemer (Mytesi)	Gastrointestinal chloride channel inhibitor	Antiretroviral therapy-associated diarrhea in patients with HIV	Upper respiratory infection, bronchitis, cough, bilirubin elevation
Lactase	Enzyme	Lactase deficiency or intolerance	Well tolerated
Loperamide	μ-Receptor agonist	Mild to moderate noninvasive diarrhea; adjunctive to other non-opiate therapies	Minimal CNS effects; avoid if suspected invasive infection; pregnancy category B
Octreotide	Antisecretory suppression of hormone release	Treatment of tumor-associated diarrhea (VIPoma [Verner-Morrison syndrome], carcinoid); HIV-associated diarrhea	Hyperglycemia, gallstone formation
Opiates, tincture of opium, diphenoxylate plus atropine	μ-Receptor agonist	Moderate to severe noninvasive diarrhea; suboptimal response to loperamide or bismuth; refractory diarrhea	CNS effects, respiratory depression; constipation, possible anticholinergic effects with atropine; avoid if suspected invasive infection
Probiotics (*Lactobacillus*, *Saccharomyces* spp.)	Competition with pathogenic organisms, production of antimicrobial substances, enhancement of immune response	Prevention of antibiotic-associated diarrhea; adjunctive therapy for treatment of *C. difficile*; small intestinal bacterial overgrowth	Well tolerated; caution if severely immunocompromised
Teduglutide (Gattex)	GLP-2 analog	Approved for adult patients with short bowel syndrome who are dependent on parenteral support	Colonic neoplasms (colonoscopy recommended every 5 yr); intestinal obstruction; biliary/pancreatic disease (bilirubin, amylase, lipase, alkaline phosphatase, every 6 mo)

CNS = central nervous system; GLP-2 = glucagon-like peptide-2.

X. CONSTIPATION

A. Definition and pathophysiology
   1. Bowel symptoms (e.g., difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) may occur in isolation or secondary to another underlying disorder. The 2013 guidelines distinguish between normal-transit constipation and slow-transit constipation. Another definition is "a symptom based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both." (Am J Gastroenterol 2014;109:S2-26)
   2. May also be characterized by difficulty with or incomplete evacuation, straining, or presence of hard, dry stools. Abdominal pain and distension can occur, as well as low back pain and anorexia.
   3. Pathophysiology is related to many different factors. Common causes include:
      a. Altered motility (e.g., ileus)
      b. Neurogenic causes (autonomic neuropathies, Parkinson disease)
      c. Endocrine or metabolic disorders (e.g., hypothyroidism, diabetes, hypokalemia, hypercalcemia, uremia)
      d. Pregnancy
      e. Psychogenic causes
      f. Structural abnormalities or obstruction
      g. Nutritional (e.g., reduced fiber and water intake)
      h. Medications (Box 7)
   4. Constipation that is not caused by an underlying organic cause is called *chronic idiopathic constipation* (CIC) or functional constipation.

Box 7. Common Causes of Drug-Induced Constipation

Aluminum-containing drugs (antacids, sucralfate)
Antihistamines
Benzodiazepines
Bile acid sequestrants
Calcium channel blockers
Calcium supplements and antacids
Diuretics
Iron supplements
Opioids
Phenothiazines
Scopolamine, benztropine
Tricyclic antidepressants

B. Diagnosis
   1. Evaluate patient history thoroughly.
      a. Establish patient baseline and evaluate for disease- and drug-induced causes.
      b. Assess fluid and electrolyte status, thyroid function
      c. Imaging (abdominal CT scan or radiograph) may be necessary to assess for ileus, obstruction, or dilatation.
   2. Referral for further evaluation may be necessary for some patient populations.
      a. Symptoms for more than 1–2 weeks despite treatment
      b. Considerable pain or cramping
      c. Pregnancy
      d. Presence of fever
      e. Blood in the stool
      f. Reduction in stool caliber
      g. Weight loss
      h. Paraplegia, quadriplegia
   3. Diagnosis of CIC (functional constipation) is based on the Rome IV criteria, which is presence of two or more of the following over the previous 3 months:
      a. Straining during at least 25% of defecations
      b. Lumpy or hard stools in at least 25% of defecations
      c. Sensation of incomplete evacuation for at least 25% of defecations
      d. Sensation of anorectal obstruction or blockage for at least 25% of defecations
      e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
      f. Fewer than three defecations per week

C. Treatment strategies
   1. Remove or treat underlying causes, if possible.
   2. Nonpharmacologic interventions
      a. Increase fluid intake to 6–8 glasses of water per day, although minimal evidence to support efficacy if dehydration is not present.
      b. Increase dietary fiber to 20–30 g/day.
      c. Incorporate or increase exercise to 3–5 days/week.
      d. Modifying behaviors: Toilet training and toileting position
   3. Drug therapy for prevention and treatment of constipation (Table 29)
      a. Choose drug therapy on the basis of desired onset of action, patient preference, presence of potential contraindications, and use in special populations.
      b. Provide patient education on alternative dose forms (enema, suppository).

Table 29. Drug Therapy Options for Treatment and Prevention of Constipation

Drugs	Role	Comments
Saline osmotic laxatives		
Magnesium citrate, magnesium hydroxide, sodium phosphate	Acute or intermittent constipation, preoperative or preprocedure bowel preparation	Fast onset (15 min to 3 hr); avoid in renal impairment, HF, cirrhosis; FDA warning regarding oral sodium phosphate and development of acute phosphate nephropathy (avoid use for bowel preparations)
Osmotic laxatives		
Glycerin	Management of acute or intermittent constipation; used in pediatric patients	Suppository; fast onset (within 1 hr)
Lactulose	Management of acute, intermittent, or chronic constipation, including CIC; useful in concomitant in chronic liver disease	Onset 1–2 days (may require multiple doses); associated with gas and bloating; syrup or powder for solution
Polyethylene glycol	Acute or chronic constipation; effective for CIC; preoperative/ colon preparation	Onset 1–3 days; safe in renal and hepatic disease and pregnancy; overall, well tolerated; may be used long term
Lactitol (Pizensy)	Management of CIC in adults	Dose: Measure 20 g of powder into a glass. Add 4 to 8 ounces of water or other common beverage (juice, coffee, tea, soda) and stir to dissolve. Drink the entire contents of the glass once daily. If persistent loose stools occur, reduce the daily dose to 10 g of powder. Separate lactitol dose from other oral medications by at least 2 hours.
Stimulant laxatives		
Bisacodyl	Short-term relief of acute or intermittent constipation or as part of preoperative or colonoscopy bowel preparation	Oral onset 6–12 hr, suppository within 1 hr; oral tablets are enteric coated
Senna	Short-term relief of acute or intermittent constipation; often used long term for prevention of opioid-induced constipation	Tablet and liquid; onset 6–12 hr; can cause abdominal cramping, electrolyte disturbances, melanosis coli

Table 29. Drug Therapy Options for Treatment and Prevention of Constipation *(continued)*

Drugs	Role	Comments
Bulk-forming laxatives		
Psyllium inulin Inulin Wheat dextrin Calcium polycarbophil Methylcellulose	Intermittent or chronic constipation	Onset 12–72 hr; less effective in drug-induced constipation and STC; requires adequate water intake to be effective; several formulations; soluble forms can be incorporated into foods, liquids, and recipes; safe in renal and hepatic disease, pregnancy, geriatrics; can cause gas and bloating. Soluble fiber with low fermentability (i.e., psyllium) is associated with fewer adverse effects such as bloating, flatulence, and abdominal discomfort
Guanylate cyclase-C agonist		
Linaclotide (Linzess)	FDA approved for IBS-C and CIC	Guanylate cyclase-C agonist: Increases fluid secretion and transit time 145- and 290-mcg capsules IBS-C: 290 mcg orally once daily; for CIC: 145 mcg orally once daily Take on empty stomach 30 min before meal; common adverse effects include diarrhea, abdominal pain, flatulence, and abdominal distension; contraindicated in pediatric patients < 6 yr and in mechanical obstruction; avoid in patients 6–17 yr of age; pregnancy category C
Plecanatide (Trulance)	FDA approved for IBS-C and CIC in adults	Guanylate cyclase-C agonist; increases fluid secretion and transit time; 3 mg tablet once daily can be crushed and administered in applesauce or water or via feeding tube; common adverse effect is diarrhea; however, significantly less common than with linaclotide Contraindicated in pediatric patients < 6 yr and in mechanical obstruction; avoid in patients 6–17 yr old
Peripheral opioid antagonist		
Methylnaltrexone (Relistor)	FDA approved for OIC in palliative care patients and for OIC in adult patients with noncancer pain	Peripheral opiate antagonist; will not reverse central analgesia OIC with advanced illness: Subcutaneous injection every other day as needed, dose based on patient weight Onset within 4 hr in about 50% of patients OIC with non cancer pain: Oral tablet 450 mg once daily or 12 mg subcutaneous injection daily

Table 29. Drug Therapy Options for Treatment and Prevention of Constipation *(continued)*

Drugs	Role	Comments
Peripheral opioid antagonist *(continued)*		
Naldemedine (Symproic)	FDA approved for OIC in adult patients with non-cancer-related pain who do not require frequent opioid dose escalation	Peripheral mu-opioid receptor antagonist 0.2 mg once daily Avoid use with strong CYP3A inducers. Monitor for naldemedine toxicity with concomitant moderate and strong CYP3A inhibitors and P-glycoprotein inhibitors
Naloxegol (Movantik)	FDA approved for OIC in adult patients with noncancer pain	Peripheral μ-opioid receptor antagonist 12.5- and 25-mg capsules; adjust dose for CrCl < 60 mL/min/1.73 m^2; contraindicated with use of strong CYP3A4 inhibitors or in patients with obstruction
Alvimopan (Entereg)	FDA approved for accelerating gastrointestinal recovery after surgeries that include partial bowel resection with primary anastomosis	Peripheral μ-opioid receptor antagonist 12 mg prior to surgery then 12 mg twice daily until discharge, maximum 7 days (15 doses); long-term use associated with myocardial infarction; only available through a REMS program
Serotonin agonist		
Prucalopride (Motegrity)	FDA approved for treating CIC in adults	Unlike past serotonin agonists (cisapride, tegaserod), prucalopride is highly selective for GI serotonin receptors and has not been reported to result in cardiac adverse effects. Carries a warning for suicidal ideation
Miscellaneous agents		
Docusate sodium Docusate potassium	Prevention of opioid-induced constipation in combination with stimulant laxatives such as senna or prevention of straining in post-MI, postsurgical, and pregnant patients	Onset 1–6 days; requires adequate water intake to be effective
Lubiprostone (Amitiza)	FDA approved for CIC in adults and for IBS-C in women > 18 yr	Chloride channel (ClC-2) activator; results in intestinal fluid secretion; can reduce bloating and abdominal pain; main adverse effect is nausea; dose is 24 mcg twice daily for constipation and 8 mcg twice daily for IBS-C; need negative pregnancy test before use
Tenapanor (Ibsrela)	FDA approved for IBS-C in patients > 18 yr	Tenapanor is a sodium/hydrogen exchanger 3 inhibitor that results in increased intestinal water secretion and GI transit time. Tenapanor may reduce abdominal pain. It is not recommended in patients < 18 yr and is contraindicated in patients < 6 yr because of risks of serious dehydration

CIC = chronic idiopathic constipation; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; HF = heart failure; IBS-C = constipation-predominant irritable bowel syndrome; MI = myocardial infarction; OIC = opioid-induced constipation; REMS = Risk Evaluation and Mitigation Strategies; STC = slow-transit constipation.

XI. IRRITABLE BOWEL SYNDROME

A. Definition and pathophysiology
   1. IBS is considered a functional GI disorder and a disorder of the gut-brain interaction.
   2. Definition divides IBS into the following subtypes:
      a. Diarrhea predominant (IBS-D)
      b. Constipation predominant (IBS-C)
      c. Mixed IBS (IBS-M): Features of both IBS-D and IBS-C
      d. Unclassified (IBS-U)
   3. The pathophysiology is thought to involve alterations in both CNS and intestinal pain perception, alterations in GI motility and secretion, and contributions from current or past psychosocial factors, gas retention, and possibly previous GI infection or bacterial overgrowth.
      a. IBS is more common in women, lower socioeconomic groups, and patients younger than 50 years.
      b. Patients with IBS have significant reductions in quality of life and use more health care resources.
      c. A comorbid psychiatric illnesses, such as depression or anxiety, may be present in a sizeable percentage of patients with IBS.
   4. Symptoms: In addition to diarrhea or constipation, pain is often a component of all subtypes. Other symptoms (e.g., bloating, distension, spasm, urgency) may be present. These symptoms, together with the Rome IV diagnostic criteria that follow, help distinguish IBS from other functional GI disorders such as CIC.

B. Diagnosis
   1. Diagnosis is made by exclusion. Rule out other GI causes with a thorough workup. Evaluation of a patient's pattern of symptoms may provide insight into subtype, although patients may alternate between forms.
   2. Several diagnostic criteria and scoring systems have been developed, including the Kruis, Manning, and Rome criteria.
      a. The Rome IV criteria are used most commonly and are as follows.
         i. Recurrent abdominal pain, on average, at least one day/week in the last three months, associated with two or more of the following criteria:
            (a) related to defecation
            (b) associated with a change in frequency of stool
            (c) associated with a change in form (appearance) of stool
         ii. Symptoms should have started at least 6 months before diagnosis
      b. Guidelines recommend that if other GI diseases are excluded and no alarm features (e.g., weight loss, bleeding, anemia) are present, diagnosis of IBS can be made with confidence.
      c. The ACG guidelines also recommend:
         i. Screening for celiac disease in patients with diarrhea symptoms
         ii. No endoscopy if younger than 45 years and no alarm symptoms
         iii. No routine food allergy testing unless reproducible symptoms are present

C. Treatment strategies
   1. Treatment involves a mix of drug, diet, and gut-directed psychotherapy interventions. Cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy have all shown effectiveness in IBS.
   2. Dietary intervention involves avoidance of foods that trigger symptoms. Current guidelines recommend a trial of diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) to reduce global IBS symptoms. Low FODMAP diets consist of 3 phases: restriction for 4-6 weeks, reintroduction of FODMAP foods, and personalized diet based on the results of reintroduction.

3. Drug therapy should target main symptoms and possible psychiatric comorbidities. Combinations of drugs may be necessary for maximal effectiveness. Treatment often begins with nonpharmacologic and nonprescription therapies. Escalation to symptom-driven prescription therapies may be necessary. Choice of treatment should be based on the efficacy of a treatment for a patient's symptoms balanced with the tolerability of the therapy such as the likelihood and severity of adverse effects. Treatment of IBS-M should target the current symptoms. Symptoms of pain should be treated with gut-directed therapies listed below. Opioids should be avoided in GI pain disorders of gut-brain interaction.
    a. Antispasmodics: Used mostly for short-term relief of abdominal pain, but also to treat diarrhea in patients with IBS-D. They can be used on an as-needed or scheduled basis. Anticholinergic antispasmodics are contraindicated in patients with comorbid severe UC, GI or urinary obstructions, myasthenia gravis, and glaucoma. Current guidelines recommend against the use of antispasmodics (dicyclomine and hyoscyamine) for global IBS symptoms due to limited and outdated trial data supporting their efficacy. Guidelines support the use of peppermint oil for global IBS symptom relief.
        i. Dicyclomine (Bentyl): Anticholinergic adverse effects
        ii. Hyoscyamine (Levsin, Levsin SL), anticholinergic adverse effects
        iii. Peppermint oil: Use enteric-coated products; it can worsen GERD, but can improve symptoms in IBS and is superior to placebo.
    b. Tricyclic antidepressants: Treat pain, improve global symptoms, and slow motility in patients with IBS-D. They can be used in IBS-C but may worsen constipation
        i. Amitriptyline, nortriptyline, and imipramine are the most studied.
        ii. Therapy should begin with low doses and slowly titrated to treat IBS symptoms while minimizing adverse effects. Doses should not be increased enough to treat comorbid depression.
        iii. Potential for anticholinergic effects, sedation, CV effects, and drug interactions.
    c. SSRIs: Have been used in the past to treat abdominal pain associated with IBS. Current guidelines recommend against the use of SSRIs to treat IBS symptoms because of a lack of strong data to support the benefits of their use. SSRIs can still be used to treat comorbid depression, anxiety, or other mood disorders in the setting of IBS.
    d. Laxatives can be used for IBS-C.
        i. Psyllium has the best evidence; however, it can cause bloating and gas formation. Calcium polycarbophil can be used as an alternative bulk-forming agent. Wheat or corn bran should not be used.
        ii. Polyethylene glycol–based laxatives (MiraLAX) can increase stool frequency, but they have no effect on reductions in abdominal pain and overall symptoms in IBS. There is minimal to no bloating.
        iii. Avoid stimulant laxatives because they can worsen abdominal pain.
    e. Lubiprostone (Amitiza) approved by the FDA for IBS-C in women older than 18 years.
        i. Chloride channel activator; improves motility and possibly pain
        ii. Dose is 8 mcg twice daily with meals for IBS-C.
        iii. Nausea and diarrhea are the main adverse effects. Patients should be advised to take lubuprostone with food to minimize nausea.
    f. Linaclotide (Linzess) is approved for IBS-C.
        ii. Guanylate cyclase-C agonist: increases fluid secretion and decreases transit time
        iii. Dose is 290 mcg orally taken once daily on an empty stomach 30 minutes before meals.
        iv. Common adverse effects: diarrhea, abdominal pain, flatulence, and abdominal distension

g. Plecanatide (Trulance) is approved for IBS-C.
   i. Structural analog of uroguanylin, an endogenous guanylate cyclase-C agonist, causes an elevation in intracellular cyclic guanosine monophosphate (cGMP), stimulates secretion of chloride and bicarbonate into the intestinal lumen through activation of the cystic fibrosis transmembrane conductance regulator ion channel. Decreased activity of pain-sensing nerves appears to occur because of elevated extracellular cGMP concentration (clinical relevance of the effect on pain fibers has not been established).
   ii. Dose: 3 mg daily without regard to food
   iii. Common adverse effects: Mainly GI related. If severe diarrhea occurs, discontinue plecanatide.
   iv. Counseling points: May be crushed and administered in applesauce or water, or by feeding tube. Dispensed in a monthly blister pack

h. Tegaserod (Zelnorm) is a serotonin-4 partial agonist that is approved by the FDA for IBS-C.
   i. Improves pain, global symptoms, and motility.
   ii. Tegaserod has been approved for reintroduction to the U.S. market for adult women younger than 65 with IBS-C. It is recommended for women with one or fewer cardiovascular risk factors who have not responded adequately to secretagogue therapy.
   iii. Tegaserod is contraindicated in patients with past myocardial infarction, stroke, transient ischemic attack, or angina. It is also contraindicated in patients with a history of ischemic colitis or other intestinal ischemia.
   iv. Linaclotide, lubiprostone, plecanatide, and tegaserod not only treat constipation symptoms but also have positive effects on global IBS-C related symptoms such as abdominal pain, bloating, and flatulence.

i. Loperamide: No effects on global symptoms or pain, but reduces motility and increases stool consistency. May be used as an adjunct to other therapies in IBS-D

j. Eluxadoline (Viberzi): (C-IV) FDA approved to treat IBS-D
   i. Mu opioid receptor agonist
   ii. Dose is 100 mg PO twice daily. Reduce to 75 mg PO twice daily if no gall bladder, unable to tolerate 100 mg, concomitant OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil, antiretrovirals [atazanavir, lopinavir, ritonavir, saquinavir, tipranavir], rifampin, eltrombopag), or mild-moderate hepatic impairment.
   iii. Can cause sphincter of Oddi dysfunction. Contraindications include biliary duct obstruction, alcohol abuse (>3 drinks/day), history of pancreatitis, Child-Turcotte-Pugh class C, severe constipation, or GI obstruction
   iv. Discontinue therapy if constipation lasts for more than 4 days

k. Alosetron (Lotronex): Serotonin-3 antagonist that is approved by the FDA for IBS-D
   i. Improves global symptoms and reduces motility
   ii. Associated with the development of colonic ischemia; therefore, available only through manufacturer prescribing program. Reserved for patients who have failed conventional therapy.

l. Probiotics: Some evidence to support improvement in global symptoms, bloating, and flatulence; not enough evidence to recommend specific strains. Current guidelines suggest avoiding probiotics for global IBS symptom relief due to a lack of sufficient supporting data.

m. Antibiotics: A short course (10–14 days) of nonabsorbable antibiotic can improve global symptoms of IBS, especially bloating in IBS-D.
   i. Rifaximin 550 mg three times daily for 14 days has FDA approval for IBS-D.
   ii. Patients who respond to rifaximin and experience recurrent symptoms can receive retreatment with rifaximin.

n. Selective serotonin reuptake inhibitors (SSRIs) have been used to treat IBS in the past. Current American Gastroenterological Association guidelines recommend against their use as they do not relieve global symptoms or abdominal pain in IBS-D or IBS-C.

Patient Cases

10. A 55-year-old man with a history of chronic alcohol abuse for 25 years is evaluated in the clinic for chronic pancreatitis. For the past 2 months, he has noticed an increase in the frequency of bowel movements to four or five times daily. He describes his stools as foul smelling and slimy. During this time, he has had 14 kg of unintentional weight loss and has intermittent abdominal pain. Quantification of fecal fat indicates an excretion of 20 g every 24 hours. His albumin is 2.1 g/dL, and he weighs 61 kg. He currently takes morphine controlled-release 45 mg twice daily and oxycodone 5–10 mg every 4–6 hours as needed. What is the best course of action for this patient?
    A. Increase MS-Contin to 60 mg twice daily.
    B. Initiate dronabinol to improve appetite.
    C. Initiate pancrelipase 40,000 units per meal.
    D. Add a multivitamin to his regimen.

11. A 32-year-old woman has had intermittent crampy abdominal pain 3–5 days/week, bloating, and reduced frequency of bowel movements for the past 6 months. Before this, she had a bowel movement daily; now, she reports a bowel movement every 2–3 days. She often needs to strain to evacuate her bowels. She reports that her symptoms do not appear related to specific foods. The results of an extensive diagnostic workup are negative, and she is given a diagnosis of IBS-C. She is otherwise healthy and reports no known drug allergies. Which therapeutic intervention is best for this patient?
    A. Amitriptyline 50 mg/day.
    B. Probiotic (i.e., VSL #3) three capsules daily.
    C. Tegaserod 6 mg twice daily.
    D. Lubiprostone 8 mcg twice daily.

12. A 30-year-old woman who is 14 weeks pregnant presents with mild myalgias; a low-grade fever (temperature 99.8°F); four or five loose, watery bowel movements; and one episode of vomiting during the past 18 hours. She reports her 3-year-old daughter and several children in her day care class had the same symptoms 3 days ago. The results of a rapid influenza test are negative, her WBC is 8×10^3 cells/mm^3, and her SCr is 0.9 mg/dL. She takes a prenatal vitamin and reports no known drug allergies. She is given a diagnosis of a presumed viral gastroenteritis. What is the best treatment for this patient's diarrhea?
    A. Loperamide.
    B. Bismuth subsalicylate.
    C. Lactase.
    D. Pyridoxine.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Patients receiving PPI therapy for GERD should be reassessed for efficacy. This patient has had some improvement in frequency of symptoms, but they are still not optimally controlled despite lifestyle modifications and being adherent. There is no evidence that upper GI dysmotility is the cause of his GERD symptoms; therefore, adding metoclopramide would not be preferred (Answer A). Switching to an alternative PPI such as omeprazole (Answer C) could be tried, but typically this would be considered in the case of intolerance to another agent. Sucralfate (Answer D) has no role in GERD treatment. The GERD guidelines endorse increasing the PPI frequency to twice daily in patients with continued symptoms, making Answer B correct.

2. Answer: C

The two most common causes of PUD are *H. pylori* infection and NSAID use. This patient has a gastric ulcer with evidence of a clot (indicating recent bleeding) in the setting of NSAID use (aspirin plus ketoprofen). In addition, she is older than 60 years, which is another risk factor for an NSAID-induced ulcer and is probably contributing to her upper GI problems and anemia. The result of the rapid urease test performed on the biopsy specimen is negative, indicating the absence of *H. pylori.* First, the patient should discontinue NSAID use. The use of NSAIDs can markedly delay healing; therefore, NSAID use should be continued only if necessary. Healing of the ulcer should be facilitated by appropriate acid-suppressive therapy. Histamine-2 receptor antagonists, although effective in some instances, are less efficacious in the healing of gastric ulcers than are the PPIs, making Answer A incorrect. Because the patient has tested negative for *H. pylori,* use of an *H. pylori* eradication regimen is not necessary; therefore, Answer B is incorrect. Misoprostol, which is effective in preventing and healing ulcers, is not preferred because of the need for several daily doses, and it is poorly tolerated because of a high incidence of abdominal pain, cramping, and diarrhea; therefore, Answer D is incorrect. The dose should also be at least 600 mcg/day. Proton pump inhibitors are the preferred drugs for healing NSAID-induced ulcers because of their excellent efficacy and favorable adverse effect profile, and they are better tolerated, making Answer C correct.

3. Answer: C

The test-and-treat approach is appropriate in patients with dyspepsia thought to have *H. pylori* infections. Patients older than 45–55 years or those with alarm features should be referred for endoscopic evaluation to rule out the possibility of a more complicated disease. Ambulatory patients can be tested for *H. pylori* using various diagnostic approaches (e.g., UBT). The eradication of *H. pylori* leads to high rates of ulcer healing and minimizes ulcer recurrence. According to treatment guidelines, eradication regimens for *H. pylori* infection should include at least two antibiotics plus an antisecretory agent given for 10–14 days. This can be accomplished with triple-drug therapies containing amoxicillin (or metronidazole) plus clarithromycin in addition to a PPI. Likewise, quadruple therapy with bismuth, tetracycline, metronidazole, and a PPI can be used as a first-line treatment in penicillin-allergic patients or as a second-line treatment of initial failures of triple-drug therapy. This patient requires treatment secondary to a positive test. Answer A would be appropriate if the duration were at least 10 days. Answer B is incorrect because cephalosporins are not recommended in *H. pylori* treatment regimens. Answer D is incorrect because fluoroquinolone-based regimens should be reserved as salvage therapy for patients whose triple and quadruple therapy has failed, and the duration of 21 days is too long. Answer C is correct; quadruple therapy offers similar efficacy and is a viable first-line treatment. Patient adherence should be reinforced to maximize efficacy.

4. Answer: D

Treatment with topical aminosalicylate therapy (e.g., a suppository or enema; Answer D) is a more effective option for patients with mildly active UC with distal disease than are oral therapies (e.g., balsalazide; Answer A). Methotrexate (Answer B) has a limited role in maintaining corticosteroid-induced remission in patients with CD, but not UC. Infliximab (Answer C) would be indicated for moderate-severe UC.

5. Answer: B

This patient has moderate to severe CD involving the terminal ileum and colon. Mesalamine (Answer A), though well tolerated, is minimally effective in CD and would not be indicated for moderate to severe disease.

Budesonide (Answer C) is effective in mild-moderate CD affecting the terminal ileum and proximal colon; therefore, the disease severity and location of the disease would not fit this regimen. Adalimumab (Answer D) would be appropriate, but the dose is for maintenance and would need to be 160 mg initially for induction. Combining infliximab and azathioprine (Answer B) has been shown to result in the highest rates of remission in moderate to severe CD compared with the use of either agent alone.

6. Answer: C

Patients with cirrhosis and ascites are at risk of developing SBP, an infection of the ascitic fluid usually caused by an enteric gram-negative organism. Typical signs of infection include fever, abdominal pain, nausea, and rebound tenderness. Diagnosis is made according to clinical symptoms plus laboratory evidence. The laboratory diagnosis is by paracentesis, with identification of more than 250/mm^3 neutrophils (polymorphonuclear neutrophils) in the ascitic fluid. This patient's value is 450/mm^3. If clinical and laboratory signs and symptoms are present, antibiotic therapy directed against enteric gram-negative bacteria should be initiated immediately (Answer A). Third-generation cephalosporins such as cefotaxime and ceftriaxone are preferred (Answer C). Aminoglycosides should be avoided because of their potential to cause nephrotoxicity (Answer B). Vancomycin should be reserved for resistant gram-positive organisms (Answer B). In addition to antibiotic therapy, the use of intravenous albumin reduces the incidence of renal failure and improves in-hospital and 30-day mortality; it is indicated given that the patient's SCr is greater than 1.0 mg/dL and her BUN is greater than 30 mg/dL. The use of oral antibiotics to treat acute SBP is not well studied (Answer D); however, an oral regimen (e.g., a fluoroquinolone or trimethoprim/sulfamethoxazole daily) should be instituted and continued indefinitely after recovery to reduce the incidence of subsequent infections.

7. Answer: B

Management of overt hepatic encephalopathy should initially involve removal and treatment of precipitating factors and the use of therapies aimed at reducing ammonia concentration. Recent guidelines recommend the use of lactulose (Answer B) to rapidly reduce ammonia concentrations in the short term. Therapy can also be continued as prophylaxis against subsequent episodes, if needed. Nonabsorbable antibiotics such as rifaximin can be used, but rifaximin 550 mg twice daily (Answer A) is indicated for use in the prevention of recurrent hepatic encephalopathy and is effective when combined with lactulose. Ceftriaxone (Answer D), which would not be as effective as rifaximin, is indicated in patients with cirrhosis who present with upper GI bleeding. Although polyethylene glycol 3350 (Answer C) has shown some efficacy in the treatment of hepatic encephalopathy, the dose used in recent trials was 4 L administered over 4 hours.

8. Answer: B

This patient has a chronic HBV infection, given the elevations in ALT and AST, the presence of HBsAg, and the high concentrations of circulating HBV DNA. The patient also has evidence of severe necroinflammation on biopsy. The patient has HBeAg positivity, and a YMDD mutation is present. She appears to have compensated liver disease, given her albumin concentration, INR, and lack of ascites or encephalopathy. Given her persistently elevated liver function test results, biopsy results, and high viral load, she should receive treatment (Answer A is incorrect). Treatment with an oral reverse transcriptase inhibitor is preferred first-line therapy. Because the patient has a lamivudine-resistant organism, as evidenced by the YMDD mutation, lamivudine therapy would be ineffective (Answer C is incorrect), and a drug therapy that treats lamivudine-resistant pathogens (e.g., tenofovir or entecavir) is recommended initially. Because the patient has an elevated SCr of 1.9 mg/dL, tenofovir alafenamide is preferred to tenofovir disoproxil fumarate (Answer D is incorrect). Entecavir is a preferred agent with activity against lamivudine-resistant virus. Entecavir is also preferred for patients with compromised renal function and would be the best choice of those listed (Answer B is correct).

9. Answer: B

This patient has newly diagnosed chronic HCV infection. He does not have cirrhosis and is treatment naive. He qualifies for the currently recommended simplified treatment regimens. Patients with genotypes 1–6 without cirrhosis should receive either glecaprevir 300 mg/pibrentasvir 120 mg for 8 weeks or sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks. This patient has genotype 1a; therefore, initiating glecaprevir/pibrentasvir for 8 weeks would be most appropriate at this time (Answer

B is correct). Withholding therapy (Answer A) would not be optimal because the current guidelines recommend treatment for all patients with chronic HCV, except for those with a short life expectancy whose condition would not be altered by HCV treatment. Ledipasvir and sofosbuvir (Answer C) combination therapy is currently recommended for treatment of genotype 1a HCV, however the regimen would continue for 12 weeks, not 8 weeks. The combination of pegylated interferon, ribavirin, and sofosbuvir (Answer D) was previously recommended, but direct-acting agents are now preferred, and pegylated interferon–based therapies are no longer recommended.

10. Answer: C

This patient has signs and symptoms of maldigestion and malabsorption secondary to the loss of pancreatic exocrine function. This is manifested by the presence of steatorrhea, weight loss, and an elevated fecal fat concentration. Management should include replacement of exogenous pancreatic enzymes to facilitate nutrient digestion and absorption (Answer C). Oral pancrelipase products are pork derived and contain lipase, amylase, and protease. A typical starting dose for an adult patient should deliver 40,000–50,000 lipase units per meal, with titration based on reduction in steatorrhea and evidence of weight gain. Although chronic abdominal pain is a typical symptom of chronic pancreatitis, increasing the patient's morphine dose will not help with the symptoms related to the lack of enzymes (Answer A). Likewise, using appetite stimulants such as dronabinol will not be beneficial if enzyme therapy is not initiated (Answer B). Finally, this patient is malnourished, and a multivitamin would be beneficial; however, patients with chronic pancreatitis may need extra supplementation of fat-soluble vitamins after enzyme therapy is initiated and increased caloric intake to facilitate weight gain (Answer D).

11. Answer: D

This patient meets the criteria for IBS-C on the basis of a negative diagnostic workup and the presence of abdominal pain, bloating, and constipation for more than 3 months. Drug therapy should target the predominant symptoms. The agents most beneficial in IBS-C are bulk-forming laxatives, which improve the frequency of bowel movements and can reduce bloating, and SSRIs, which provide relief from abdominal pain, improve global symptoms of IBS, and improve motility in most patients. The tricyclic antidepressants have effects similar to the SSRIs but are associated with anticholinergic effects, which may worsen constipation. Thus, amitriptyline would not be preferred in this case (Answer A). Lubiprostone is approved for IBS-C in women older than 18 years and improves motility and possibly abdominal pain (Answer D). It is the best choice presented, given the patient's symptoms. Probiotics such as VSL #3 can improve global symptoms of IBS, but they would not improve bowel frequency; therefore, use would be best with another therapy that would increase stool frequency (Answer B). Although effective for IBS-C when it was available, tegaserod is available only on an emergency basis because of its association with the development of CV events (Answer C).

12. Answer: A

Diarrhea is caused by a variety of conditions, with viral pathogens being one of the most common causes. This patient probably developed diarrhea through contact with her daughter, who is in day care and had similar symptoms a few days earlier. In addition, her low-grade fever, myalgias, watery diarrhea, and vomiting point to a potential viral cause. Although most episodes of viral gastroenteritis are self-limited, symptomatic relief may be necessary to prevent dehydration. Antidiarrheal therapy should be selected according to patient preference and the presence of any precautions or contraindications. If this patient desires therapy, a therapy should be chosen that minimizes risk to the patient and the fetus, given that she is pregnant. Loperamide (Answer A) is an effective agent for short-term relief of diarrhea, and it carries an FDA pregnancy category B rating; therefore, it would be the best choice in this case. Use of bismuth (Answer B), although effective, should be avoided in pregnant and nursing patients because of the risk of potential toxicity. Lactase (Answer C) would be indicated only if the patient's diarrhea were secondary to lactose intolerance. Pyridoxine (Answer D) is used for the treatment and prevention of nausea and vomiting in pregnancy, but it has no effect on the treatment of diarrhea related to viral gastroenteritis.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

This patient has signs of dysphagia, an alarm symptom that is sometimes associated with a more complicated case of GERD. The patient has tried antacids with minimal relief and has a history of NSAID use. The patient is older than 45 years, which increases his risk of developing gastric cancer. Therefore, he should be referred for endoscopic evaluation to rule out a more complicated disease (Answer B). Using either H_2RAs (Answer A) or a PPI as initial therapy after endoscopic evaluation would be appropriate if the patient does not respond to antacids; however, a twice-daily dosing of PPIs (Answer C) is not necessary as initial dosing. Changing medications that reduce LES tone (e.g., calcium channel antagonists) is an appropriate recommendation for reducing GERD symptoms; this should be considered after invasive testing is performed (Answer D).

2. Answer: C

For patients beginning long-term NSAID therapy, a thorough assessment of patient- or drug-related factors that may predispose them to the development of GI toxicity is necessary. Likewise, an evaluation of the patient's level of CV risk is necessary. Given the use of low-dose aspirin for preventing CV events, this patient would be considered at high risk of CV events. Efforts to avoid GI toxicity should include the use of the GI agent that is least toxic at the lowest effective therapeutic dose. A GI-protective agent should be considered to minimize NSAID-induced erosions and ulcers. Indomethacin (Answer B) and piroxicam (Answer D) are more likely to cause GI complications than is naproxen (Answer C). Use of COX-2 inhibitors (Answer A) is acceptable in patients with rheumatoid arthritis because these agents reduce GI complications and effectively treat pain. However, this patient has CV risk factors including diabetes, hypertension, and dyslipidemia. Recent findings of increased CV events, especially with high doses of COX-2 inhibitors, would preclude their use. Therapy with an acid-suppressive agent is also an acceptable choice for GI prevention in users of nonselective NSAIDs. Proton pump inhibitors are effective for this indication (Answer C). The H_2RAs are ineffective in preventing serious NSAID-induced GI complications (Answer B). Misoprostol, although effective, is associated with a high incidence of diarrhea and abdominal pain and the need for multiple daily dosing (Answer D). Given that this patient is considered at moderate risk of GI complications, because of the patient's use of aspirin and need for high-dose NSAIDs, the use of naproxen plus a PPI would be preferred, according to the recent ACG guidelines (Answer C).

3. Answer: D

This patient presents with signs and symptoms consistent with an NSAID-induced upper GI bleed. He has several risk factors for NSAID-induced GI bleeding, including age older than 60 years, use of aspirin, and long duration of NSAID use. The presence of underlying CV disease, although not a direct risk factor, may also contribute to increases in NSAID GI toxicity. He also has many criteria that place him at high risk of rebleeding. According to the consensus recommendations for nonvariceal bleeding, he should receive an intravenous PPI by bolus and subsequent continuous infusion for 72 hours (Answer D). Note that the guidelines provided state that this therapeutic approach can be extrapolated to patients with NSAID-induced ulcers and bleeding, even though most of the data included in the guidelines pertain to non–NSAID-induced causes of upper GI bleeding. He will then require treatment with an appropriate dose of an oral PPI for at least 8 weeks; after that, he should be assessed for possible continued prophylactic use. H2RAs (Answer A) are less efficacious for the treatment and prevention of rebleeding for NSAID-induced ulcers. Sucralfate (Answer B) has minimal efficacy in the setting of acute GI bleeding. Oral PPIs (Answer C) are effective in preventing and healing NSAID-induced ulcers; however, in this case, the lansoprazole dose is inadequate for treatment. Oral PPIs should be used at an appropriate dose after intravenous therapy.

4. Answer: D

Given this patient's presenting symptoms, she would be classified in the mild active disease category. First-line therapy for active extensive disease would consist of an oral aminosalicylate at a dose equivalent to mesalamine at least 2 g/day. A product such as Delzicol (Answer D) is formulated to release mesalamine in the colon, which would be appropriate in this case. Sulfasalazine (Answer A) has reported efficacy for this indication and is activated in the colon; however, this patient reports

a life-threatening allergy to sulfonamide-containing medications. Topical therapy with hydrocortisone enema (Answer B) would be appropriate if the patient had disease distal to the splenic flexure. Immune modulators such as mercaptopurine (Answer C) have a long onset of action (3–15 months) and are not appropriate for acute active disease.

5. Answer: B

Primary prophylaxis of bleeding should be instituted in patients with large varices and cirrhosis. Nonselective β-blockers are appropriate as first-line therapy. Therapy should be targeted to achieve a resting heart rate of 55 beats/minute or a 25% reduction from baseline. The patient has taken propranolol for 1 month and has not met these goals (Answer A). Because he is tolerating propranolol, the dose should be increased (Answer B), and he should be observed to reassess the need for further dosage adjustments. Adding a nitrate (Answer C) would increase the reduction in portal pressures; however, nitrates have not been shown to improve mortality. Most patients have an increased risk of adverse effects with this combination. Nonselective β-blockers are preferred to cardioselective agents (Answer D) because antagonism of the β-receptor prevents splanchnic vasodilation.

6. Answer: C

The sensitivity of a test can be thought of as the proportion of patients with a disease who have a positive test, whereas specificity deals with the proportion of patients without the disease who have a negative test. Calculating these values is accomplished by establishing a 2 × 2 table representing the results of the test. The sensitivity can be calculated by dividing the number of patients having the disease using the new test who were also positive using a gold standard test (true positives), which in this case is 850, by the number of patients receiving a diagnosis of having the disease using the gold standard, which in this case is 900. The 900 represents the true positives and 50 patients with the disease but without the diagnosis of it, according to the new test (false negatives). Specificity can be calculated by taking the number of patients not having the disease using the gold standard who tested negative with the new test (true negatives = 85). Next, divide this result by the number of patients who truly had no disease using the gold standard, 100, which incorporates the 15 patients who tested positive with the new test but truly had no disease (i.e., false positives). Sensitivity = 850/(850 + 50) = 94%; specificity = 85/(85 + 15) = 85%. (Answer C). The other numerical manipulations possible are not representative of sensitivity and specificity (Answers A, B, and D).

Result	Infection	No Infection	Total
Positive	850	15	865
Negative	50	85	135
Total	900	100	1000

7. Answer: C

Postexposure therapy for HAV may be offered to restaurant patrons if a food handler at a restaurant is documented to have HAV and is considered infectious while handling food. The most effective therapies for postexposure prophylaxis are administration of HAV immune globulin or vaccine. The efficacy of the vaccine approaches that of immune globulin, but only in patients younger than 40 years, according to the Centers for Disease Control and Prevention guidelines. The period for administration should be within 14 days of exposure; therefore, this patient does not meet the criteria for receiving HAV immune globulin (Answer B) or vaccine (Answer A). She should be observed for signs and symptoms of active disease (Answer C). Hepatitis A vaccine should be offered to patients as preexposure therapy if they are considered at risk of exposure to HAV. The combination of vaccine and immune globulin for postexposure therapy is unnecessary (Answer D).

8. Answer: C

This patient presents with elevated aminotransferases, consistent with alcoholic hepatitis. Prognosis of alcoholic hepatitis can be initially evaluated with the Maddrey discriminant function (MDF) score, calculated as 4.6 × (Patient's PT − Control PT) + Total bilirubin (mg/dL), where *PT* is prothrombin time. Patients whose score is greater than 32 are believed to have a poor prognosis. This patient's MDF score is 42.5; therefore, she would qualify for treatment with a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper (Answer C). This can lead to a 30% decrease in the risk ratio of short-term death. Naproxen (Answer A), though having anti-inflammatory activity, has no role in the treatment of alcoholic hepatitis and may precipitate acute kidney injury in patients with liver disease; therefore, it should be avoided. Octreotide (Answer B) would be indicated in the setting of acute

variceal bleeding, and midodrine (Answer D) is indicated for hepatorenal syndrome. This patient has no evidence of either condition.

9. Answer: D

The treatment used in this case for chronic HCV, genotype 3 with compensated cirrhosis and NS5A resistance-associated substitutions is the fixed-dose combination of sofosbuvir 400 mg/velpatasvir 100 mg with the addition of ribavirin. Alternatively, sofosbuvir/velpatasvir/voxilaprevir may be considered. Genotype 2 responds well to therapy. Although this patient appears to be responding to treatment, as indicated by reductions in aminotransferases and HCV RNA, the earliest that HCV RNA should be evaluated is 4 weeks, not 2 weeks (Answer A). This patient does not appear to have adverse effects to sofosbuvir (Answer B) or symptoms consistent with extrahepatic manifestations of HCV (e.g., glomerulonephritis or rheumatologic disorders; Answer C). The patient does have evidence of hemolysis, including scleral icterus, rapid decline in hematocrit, fatigue, and elevated indirect bilirubin, probably representing hemolytic anemia secondary to ribavirin, which commonly occurs within the first 2 weeks of therapy (Answer D). Furthermore, there is no evidence that the decrease in hematocrit is secondary to bleeding.

10. Answer: A

Infliximab is an appropriate agent for the treatment of fistulizing CD. Because of its effects on TNF, latent infections such as tuberculosis can become reactivated during therapy. Therefore, patients should have a purified protein derivative or QuantiFERON-TB test to rule out underlying tubercular disease before treatment is initiated (Answer A). Although infliximab therapy is associated with infusion-related reactions, administering a test dose is not routinely recommended (Answer B). Infliximab may be administered in a clinic setting; it does not require admission to the hospital for monitoring (Answer C). Infliximab therapy is associated with exacerbations of underlying heart failure and is contraindicated in patients with New York Heart Association class III or IV disease. This patient is young, with no history of heart failure and no clinical signs of heart failure. Therefore, a baseline echocardiogram is not necessary to assess cardiac function (Answer D).

11. Answer: C

Treatment of nausea and vomiting in medical inpatients can be accomplished by administering a variety of antiemetics. Nausea and vomiting are common symptoms associated with pyelonephritis, and they will subside once appropriate antibiotic therapy adequately treats the infection. However, patients will need symptomatic relief until the antibiotics take effect. Agents typically used for medical inpatients include phenothiazines and serotonin antagonists. The use of intravenous or rectal formulations is usually preferred for patients with severe nausea, such as this patient. Ondansetron (Answer C) is a serotonin antagonist that can be administered as needed intravenously and is effective in treating nausea caused by a variety of medical conditions. Despite its effects on serotonin, it should not cause any significant interaction with the patient's sertraline dose. Prochlorperazine (Answer A), a commonly used antiemetic, would be a viable option; however, using the oral product in this case would not be preferred, given that the patient has severe vomiting. In addition, prochlorperazine is a dopamine antagonist, and the patient is receiving a high dose of risperidone. This combination can lead to the development of EPS and, in severe cases, QTc prolongation. Metoclopramide (Answer B) is typically used as an antiemetic when gastroparesis is present or as an adjunctive therapy for patients whose other therapies have failed. Metoclopramide also has dopamine antagonist effects that can lead to the development of EPS. Diphenhydramine (Answer D) is more effective for nausea related to motion sickness, but it would not effectively treat severe short-term nausea or the other options.

12. Answer: B

This patient presents with acute constipation given his symptoms of abdominal pain, both by complaints and on examination; reduced frequency of bowel movements; and radiographic evidence of a large quantity of stool in the colon. Contributing factors include the use of verapamil and oxycodone without the use of a drug regimen to prevent constipation. Therapy should be instituted to provide a quick onset to initiate a bowel movement and provide symptom relief. Saline laxatives such as sodium phosphate (Answer A) provide quick results, especially when given by enema. The oral formulation of sodium phosphate results in phosphate absorption and is problematic in patients with chronic kidney disease. This patient's CrCl is about 34 mL/

minute/1.73 m^2, so saline laxatives should be avoided. Bisacodyl suppositories (Answer B) provide rapid stimulation of the lower intestinal tract without the risk of electrolyte absorption, so they would be preferred in this case. Methylcellulose (Answer C) is a bulk-forming laxative that would not treat the patient's acute constipation, but it would be an option for preventing constipation on a long-term basis in this patient once the short-term episode is resolved. Although methylnaltrexone (Answer D) is indicated for opioid-induced constipation, it would generally not be used as first-line agent, given the need for injection and the added cost compared with traditional laxatives.

13. Answer: D

Stress-related mucosal disease develops in critically ill patients and can lead to significant upper GI bleeding. Therapy initiation to prevent SRMD is based on the presence of risk factors. Independent risk factors include mechanical ventilation and coagulopathy. This patient is currently receiving mechanical ventilation and has other risk factors such as sepsis, hypotension, and acute renal insufficiency; therefore, he would meet the criteria for initiating pharmacologic prophylaxis. Both H_2RAs and PPIs are viable first-line options. Cimetidine (Answer C) carries an FDA-approved indication for the prevention of SRMD; however, the dosing provided is incorrect because 50 mg/hour is the approved dose. Likewise, cimetidine would need to be dose adjusted for the patient's CrCl, which can be assumed less than 10 mL/minute/1.73 m^2. Pantoprazole (Answer D) would be a better choice in this case, and it does not require adjustment for the CrCl. Sucralfate (Answer A) has historically been used to prevent SRMD, but it has fallen out of favor because of the need for multiple daily dosing and the risk of aluminum accumulation in patients with kidney disease. Antacids such as magnesium hydroxide (Answer B) are not as effective as H_2RAs, require multiple daily dosing, and are associated with electrolyte accumulation in patients with kidney injury.

14. Answer: D

Several different forms of bias exist that can adversely affect the validity or results of a trial. Errors in sampling or measurement, incorrect patient enrollment methods, and differences in patient populations studied in a trial are examples of areas of study design and conduction that may introduce bias. When evaluating drug literature, an important aspect of deciding whether the reported results are valid is to recognize important causes of bias. A retrospective cohort design typically uses medical records to evaluate events that occurred in the past after exposure to a drug. Recall bias (Answer A) pertains to study outcomes or events that patients are asked to recall, with results differing depending on the ability of patients to remember an event. For this study, objective documentation of ulceration or bleeding was performed to make comparisons between groups, eliminating patient recall as a potential bias. Misclassification bias (Answer B) is typically problematic in case-control studies, in which patients can be entered in the case study group but have not actually been exposed to the drug in question, which would not be applicable in this case. Interviewer bias (Answer C), or observer bias, is typically problematic in direct patient survey studies; it pertains to variation in the way different investigators collect data within a trial. To eliminate this bias, everyone involved in data collection in a study should be trained in the same manner of data collection to maintain consistency. Again, because an objective measure of GI toxicity was recorded by endoscopy, the possibility of interviewer bias is minimized. Channeling bias (Answer D) is a form of allocation bias in which medications with similar therapeutic indications are administered to patients with differing prognoses or risk levels. Should claims be made that a new drug introduced to a therapeutic class has a particular advantage—in this case, a safer GI toxicity profile—the chance that use will be channeled to high-risk patients is much greater. Given that the drug may be studied in higher-risk patients rather than those in the comparator group, the development of more events in this newer drug group may mask potential differences in safety and cause these events to be attributed to drug-induced toxicity.

15. Answer: B

Positive predictive value gives the proportion of patients with a disease when the presence of the disease is indicated by a diagnostic test. It is affected by disease prevalence; thus, as disease prevalence falls, so does the positive predictive value of the test. Using the sensitivity, specificity, and prevalence, a 2 × 2 table can be constructed. The positive predictive value is calculated by dividing the true positives by the sum of the true and false positives. In this case, that would be 190/(190 + 24) × 100 = 89% (Answer B). The total number of patients who tested positive divided by the number

who tested negative, 75% (Answer A), does not indicate the positive predictive value of a test. Specificity deals with the proportion of patients without the disease who have a negative test result; it can be calculated by taking the number of patients not having the disease using the gold standard who tested negative with the new test (true negatives = 276). Next, divide this by the number of patients who truly had no disease using the gold standard, 300, which incorporates the 24 patients who tested positive with the new test but truly had no disease (i.e., false positives). Specificity = 276/(276 + 24) = 92% (Answer C). The number of patients who tested negative and had no infection divided by the total number of patients with no infection does not illustrate positive predictive value 276/(276 + 10) = 96% (Answer D).

Result	Infection	No Infection	Total
Positive	190	24	214
Negative	10	276	286
Total	200	300	500

Endocrine and Metabolic Disorders

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Learning Objectives

1. Differentiate between the diagnostic and classification criteria for various endocrine and metabolic disorders, including type 1 and type 2 diabetes, diabetes insipidus, polycystic ovary syndrome, obesity, and disorders of the thyroid, adrenal, and pituitary glands.
2. Discriminate between the various therapeutic agents used in treating endocrine and metabolic disorders.
3. Select appropriate treatment and monitoring options for a given patient presenting with one of the previously mentioned endocrine or metabolic disorders.
4. Recommend appropriate therapeutic management for secondary complications from diabetes or thyroid disorders.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
A1C	Hemoglobin A1C
ACTH	Adrenocorticotropic hormone
ARB	Angiotensin receptor blocker
BG	Blood glucose
BMI	Body mass index
DI	Diabetes insipidus
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GH	Growth hormone
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
SGLT-2	Sodium glucose cotransporter-2
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TDI	Total daily insulin
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 66-year-old Hispanic man (weight 123.8 kg; body mass index [BMI] 42 kg/m^2) with a history of dyslipidemia and hypertension received a diagnosis of type 2 diabetes (T2D). After 1 month of exercise and dietary changes and no diabetes medications, his hemoglobin A1C (A1C) and fasting glucose concentration today are 11.5% and 362 mg/dL, respectively. Which set of drugs is best to initiate?
   A. Metformin and glipizide.
   B. Glipizide and insulin glulisine.
   C. Pioglitazone and acarbose.
   D. Insulin detemir and glulisine.

2. A patient weighing 65 kg with symptoms of hyperglycemia and a fasting glucose concentration of 298 mg/dL is given a diagnosis of type 1 diabetes (T1D). The patient's physician asks for a recommendation of an appropriate starting dose of basal insulin and estimates the total daily insulin (TDI) needs of 0.4 unit/kg/day. Which recommendation is most appropriate?
   A. 13 units of insulin detemir.
   B. 13 units of insulin aspart.
   C. 26 units of insulin glargine.
   D. 26 units of insulin glulisine.

3. A patient with T2D has a blood pressure reading of 152/84 mm Hg, a serum creatinine (SCr) of 1.8 mg/dL, and two recent random urine albumin/creatinine concentrations of 420 and 395 mg/g. Which class of drugs (barring any contraindications) is best to initiate in this patient?
   A. Thiazide diuretic.
   B. Dihydropyridine calcium channel blocker.
   C. Angiotensin receptor blocker (ARB).
   D. Non-dihydropyridine calcium channel blocker.

4. Regarding propylthiouracil and methimazole in the treatment of hyperthyroidism, which statement is most appropriate?

A. Propylthiouracil is clinically superior to methimazole in efficacy.

B. Propylthiouracil may be associated with greater liver toxicity than methimazole.

C. Both agents are equally efficacious in the treatment of Hashimoto disease.

D. Both medications should be administered three times daily.

5. Which medication is most appropriate for a patient with a diagnosis of Cushing syndrome who has had inadequate symptom relief after surgical resection for a pituitary adenoma?

A. Ketoconazole.

B. Spironolactone.

C. Hydrocortisone.

D. Bromocriptine.

6. A physician asks for a recommendation of initial therapy for a patient with T2D. The physician states that metformin is no longer an option for this patient. An A1C obtained today is 9.4% (personal goal 7%), and the patient's estimated glomerular filtration rate (eGFR) is 29 mL/minute/1.73 m^2. Which agent would be the best recommendation?

A. Canagliflozin.

B. Alogliptin.

C. Insulin glargine.

D. Exenatide.

7. A 76-year-old woman (weight 47 kg) recently given a diagnosis of Hashimoto disease presents with mild symptoms of lethargy, weight gain, and intolerance to cold. Her thyroid-stimulating hormone (TSH) is 12.2 mIU/L and free thyroxine (T_4) is below normal limits. She has a history of hypertension and underwent a coronary artery bypass surgery 2 years ago. Which would be the most appropriate initial treatment for this patient?

A. Levothyroxine 25 mcg once daily.

B. Levothyroxine 75 mcg once daily.

C. Liothyronine 25 mcg once daily.

D. Liothyronine 75 mcg once daily.

8. A woman with T2D has an A1C of 8.6%. She is receiving insulin glargine (60 units once daily at bedtime) and insulin aspart (8 units before breakfast, 7 units before lunch, and 12 units before dinner). She is consistent in her carbohydrate intake at each meal. Her morning fasting plasma glucose (FPG) and premeal blood glucose (BG) readings have consistently averaged 112 mg/dL. Her bedtime readings are averaging 185–200 mg/dL. Which is the best insulin adjustment to improve her overall glycemic control?

A. Increase prebreakfast aspart to 10 units.

B. Increase predinner aspart to 14 units.

C. Increase bedtime glargine to 65 units.

D. Increase prelunch aspart to 9 units.

9. A 53-year-old woman with a history of Graves disease had ablative therapy 3 years ago, after which she had significant symptom relief and became euthyroid. Her thyroid laboratory values today include TSH 0.12 mIU/L and free T_4 3.8 g/dL. She states that many of her previous symptoms have returned but are mild. Which would be the most appropriate treatment for her condition?

A. Methimazole.

B. Lugol's solution.

C. Propylthiouracil.

D. Metoprolol.

10. A 65-year-old man with T2D has received metformin 1000 mg twice daily for the past 2 years. His A1C today is 7.8%. His morning FPG readings are consistently at goal. His after-meal glucose readings average 190–200 mg/dL. Which would be most appropriate for this patient?

A. Increase metformin to 1000 mg three times daily.

B. Add insulin glargine 10 units once daily.

C. Change from metformin to insulin glargine 10 units once daily.

D. Add saxagliptin 5 mg once daily.

11. A 34-year-old woman has a BMI of 33 kg/m^2. With dietary changes, she has lost 0.9 kg (2 lb) in 6 months. She exercises regularly but cannot do more because she has two jobs and young children.

Her medical history is significant for depression, T2D, and substance abuse. Her current medications include metformin 1000 mg twice daily, insulin glargine 24 units once daily, and sertraline 100 mg once daily. Her A1C is well controlled, but she occasionally has hypoglycemic episodes. She is most concerned about weight loss. Which would be the best recommendation to help her lose weight?

A. Continue her diet and exercise routine; additional intervention is unwarranted.

B. Initiate liraglutide 3 mg once daily.

C. Initiate phentermine/topiramate 3.75/23 mg once daily.

D. Initiate orlistat 120 mg three times daily with meals.

12. A 53-year-old Hispanic woman has a BMI of 44 kg/m^2 and a history of gestational diabetes. Her mother and sister both have T2D. Two weeks ago, her A1C was 7.4%. Her fasting glucose concentration today is 178 mg/dL. She is asymptomatic. Which is the best course of action?

A. Diagnose T2D and begin treatment.

B. Diagnose T1D and begin treatment.

C. Obtain another A1C today.

D. Obtain another glucose concentration another day.

13. A 42-year-old man has a history of T2D. His current therapy includes metformin 1000 mg twice daily, glyburide 10 mg twice daily, and aspirin 81 mg once daily. Today, his A1C is 6.9%, blood pressure is 126/78 mm Hg, and fasting lipid panel is as follows: total cholesterol 212 mg/dL, low-density lipoprotein cholesterol (LDL) 98 mg/dL, high-density lipoprotein cholesterol (HDL) 45 mg/dL, and triglycerides (TG) 145 mg/dL. Which would be most appropriate for this patient?

A. Add insulin detemir 10 units once daily.

B. Add lisinopril 10 mg once daily.

C. Add atorvastatin 10 mg once daily.

D. Add fenofibrate 145 mg once daily.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.1, 1.1.2, 1.1.3, 1.1.6, 1.1.8, 1.1.10, 1.1.13, 1.1.14, 1.1.15
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.1, 1.2.4, 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1, 1.3.3, 1.3.4, 1.3.5

Systems and Patient Care Problems

In addition, this chapter covers the following systems and patient care problems:

1. Thyroid disorders
2. Diabetes insipidus
3. Pituitary gland disorders
4. Adrenal gland disorders
5. Obesity
6. Polycystic ovary syndrome
7. Diabetes (types 1 and 2)
8. Treatment of DM complications

I. THYROID DISORDERS

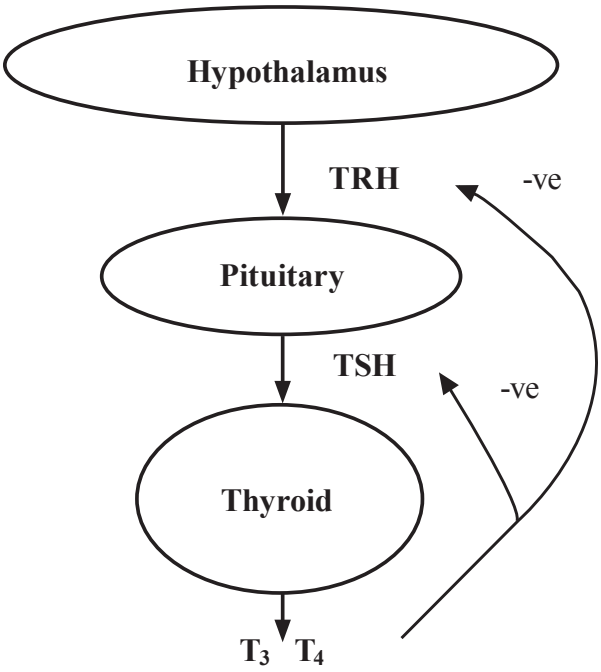

Figure 1. Hypothalamus-pituitary-thyroid axis.

[a]T_4 is converted to T_3 by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.

T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; -ve = negative feedback loop.

Patient Case

1. A 43-year-old non-pregnant woman has received a diagnosis of Graves disease. She is reluctant to try ablative therapy and wants to try oral pharmacotherapy first. Her thyroid laboratory values today include TSH 0.22 mIU/L (normal 0.5–4.5 mIU/L) and free T_4 3.2 ng/dL (normal 0.8–1.9 ng/dL). She is anxious and always feels warm when others say it is too cold. Which is best for initial treatment of her condition?
   A. Lugol's solution.
   B. Propylthiouracil.
   C. Atenolol.
   D. Methimazole.

A. Hyperthyroid Disorders (thyrotoxicosis)
   1. Classification
      a. Toxic diffuse goiter (Graves disease): Most common hyperthyroid disorder
         i. Autoimmune disorder
         ii. Thyroid-stimulating antibodies directed at thyrotropin receptors mimic TSH and stimulate triiodothyronine (T_3) and thyroxine (T_4) production.
      b. Pituitary adenomas: Produce excessive TSH secretion that does not respond to normal T_3 negative feedback
      c. Toxic adenoma: Nodule in thyroid, autonomous of pituitary, and TSH
      d. Toxic multinodular goiter (Plummer disease): Several autonomous follicles that, if large enough, cause excessive thyroid hormone secretion

e. Painful subacute thyroiditis: Self-limiting inflammation of the thyroid gland caused by viral invasion of the parenchyma, resulting in the release of stored hormone
f. Drug induced (e.g., excessive exogenous thyroid hormone dosages, amiodarone therapy)

2. Diagnosis
   a. Elevated free T_4 serum concentrations
   b. Suppressed TSH concentrations (except in TSH-secreting adenomas)
   c. If examination and history do not provide the exact etiology, radioactive iodine uptake can be used.
      i. Radioactive iodine uptake elevated if thyroid gland is actively and excessively secreting T_4 and/or T_3: Graves disease, TSH-secreting adenoma, toxic adenoma, multinodular goiter
      ii. Radioactive iodine uptake is suppressed in disorders caused by thyroiditis or hormone ingestion.
   d. Can also assess for the presence of various thyroid-related antibodies (thyroid stimulating, thyrotropin receptor, or thyroperoxidase), thyroglobulin, and thyroid biopsy
3. Clinical presentation
   a. Weight loss or increased appetite
   b. Lid lag
   c. Heat intolerance
   d. Goiter
   e. Fine hair
   f. Heart palpitations or tachycardia
   g. Nervousness, anxiety, insomnia
   h. Menstrual disturbances (lighter or more infrequent menstruation, amenorrhea) caused by hypermetabolism of estrogen
   i. Sweating or warm, moist skin
   j. Exophthalmos, also known as opthalmopathy or thyroid eye disease
4. Therapy goals
   a. Minimize or eliminate symptoms, improve quality of life
   b. Minimize long-term damage to organs (heart disease, arrhythmias, sudden cardiac death, bone demineralization, and fractures)
   c. Normalize free T_4 and TSH concentrations
5. Therapeutics
   a. Ablative therapy: Common treatment for Graves disease, toxic nodule, multinodular goiter; radioactive iodine ablative therapy and surgical resection for adenomas according to patient preferences or comorbidities. Ablative therapy often results in hypothyroidism.
   b. Thyroidectomy
   c. Antithyroid pharmacotherapy can be used for:
      i. Those awaiting ablative therapy or surgical resection
         (a) Depletes stored hormone
         (b) Minimizes risk of posttreatment hyperthyroidism caused by thyroiditis
      ii. Those who are not ablative or surgical candidates (e.g., serious cardiovascular disease, candidate unlikely to be adherent to radiation safety)
      iii. When ablative therapy or surgical resection fails to normalize thyroid function
      iv. Those with a high probability of remission with oral therapy for Graves disease
         (a) Mild disease
         (b) Small goiter
         (c) Low or negative antibody titers
         (d) Women
      v. Those with limited life expectancy
      vi. Those with moderate to severe active Graves ophthalmopathy

d. Thioureas (i.e., propylthiouracil, methimazole)
   i. Mechanism of action: Inhibits iodination and synthesis of thyroid hormones; propylthiouracil can block T_4/T_3 conversion in the periphery as well at high doses
   ii. Dosing
      (a) Propylthiouracil
         (1) Initial: 50–150 mg by mouth three times daily
         (2) Once euthyroid, can reduce to 50 mg two or three times daily
         (3) Recommended over methimazole in the first trimester of pregnancy because of the risk of embryopathy; can change to methimazole in second trimester
      (b) Methimazole
         (1) Preferred agent for Graves disease according to the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association for most patients
         (2) Initial: 10–30 mg by mouth once daily (use higher dose in those with higher baseline free T_4 concentrations)
         (3) Once euthyroid, may reduce to 5–10 mg/day
      (c) Monthly dosage titrations as needed (depending on symptoms and free T_4 concentrations);
         (1) TSH may remain low for months after therapy begins
         (2) Early in therapy, total T_3 may be a better marker of efficacy than free T_4.
   iii. Adverse effects
      (a) Hepatotoxicity risk (boxed warning for propylthiouracil): Consider baseline liver function tests. Routine evaluation of liver function while receiving antithyroid agents has not been shown to prevent severe hepatotoxicity.
      (b) Rash
      (c) Arthralgia, lupus-like symptoms
      (d) Fever
      (e) Agranulocytosis early in therapy (usually within 3 months): Guidelines recommend a baseline complete blood cell count; no routine monitoring recommended. Can repeat if patient becomes febrile or develops pharyngitis
      (f) Acute pancreatitis with methimazole
   iv. Efficacy
      (a) Slow onset in reducing symptoms (weeks). Maximal effect may take 4–6 months.
      (b) Neither drug appears superior to the other in efficacy.
      (c) On a milligram-to-milligram basis, methimazole is 10-fold more potent than propylthiouracil.
      (d) Remission rates low: 20%–30%. Remission is defined as normal TSH and T_4 for 1 year after discontinuing antithyroid therapy.
      (e) Therapy duration in Graves disease (oral agents unlikely to cause remission in those with nodular thyroid disease)
         (1) Usually 12–18 months; length of trial might not affect remission rate
         (2) Consider trial off oral therapy if TSH is normal; antibody titers can help guide decision.
         (3) Monitor thyroid concentrations every 1–3 months for up to 12 months for relapse (abnormal TSH or T_4 return).

e. Nonselective β-blockers (primarily propranolol; sometimes nadolol)
   i. Mechanism of action: Blocks many hyperthyroidism manifestations mediated by β-adrenergic receptors; also may block (less active) T_4 conversion to (more active) T_3 when used at high doses
   ii. Propranolol dosing
      (a) Initial: 20–40 mg by mouth three or four times daily
      (b) Maximal: 240–480 mg/day

iii. Adverse effects (see Hypertension section in Chronic Care in Cardiology chapter)
iv. Efficacy
(a) Used primarily for symptomatic relief (e.g., palpitations, tachycardia, tremor, anxiety)
(b) Guidelines recommend use in all symptomatic patients, especially older adults and others with heart rates greater than 90 beats/minute or existing cardiovascular disease. Also recommended for use before ablative iodine therapy in those who are extremely symptomatic or have a free T_4 2–3 times the upper limit of normal
(c) Poor remission rates: 20%–35%
(d) Alternatives to β-blockers: Clonidine, non-dihydropyridine calcium channel blocker

f. Iodines and iodides (e.g., Lugol's solution, saturated solution of potassium iodide)
i. Mechanism of action: Inhibits the release of stored thyroid hormone. Minimal effect on hormone synthesis. Helps decrease vascularity and size of gland before surgery
ii. Dosing
(a) Lugol's solution (6.3–8 mg of iodide per drop)
(b) Saturated solution of potassium iodide (38–50 mg of iodide per drop)
(c) Potassium iodide tablets: 130 mg tablets contain 100 mg of iodide.
(d) Usual daily dose: 120–400 mg mixed with juice or water, split three times daily
iii. Adverse effects
(a) Hypersensitivity
(b) Metallic taste
(c) Soreness or burning in mouth or tongue
(d) Do not use in the days before ablative iodine therapy (may reduce uptake of radioactive iodine).
iv. Efficacy
(a) Limited efficacy after 7–14 days of therapy because thyroid hormone release will resume
(b) Primary use is temporary before surgery (7–10 days) to shrink the gland.
(c) Can be used after ablative therapy (3–7 days) to inhibit thyroiditis-mediated release of stored hormone
(d) Used acutely in thyroid storm

g. Treatment of thyroid eye disease
i. Teprotumumab: Insulin-like growth factor-1 (IGF-1) receptor inhibiting monoclonal antibody
ii. Shown to reduce proptosis (eye protrusion)
iii. Administered by intravenous injection

B. Subclinical Hyperthyroidism
1. Definition: Low (below lower limit of reference range) or undetectable TSH with normal T_4
2. Risk
a. Associated with elevated risk of atrial fibrillation in patients older than 60
b. Associated with elevated risk of bone fracture in postmenopausal women
c. Conflicting data about mortality risk
3. Treatment similar to treatment of overt hyperthyroidism
a. Oral antithyroid drug therapy alternative to ablative therapy in young patients with Graves disease
b. β-Blockers may help control cardiovascular morbidity, especially with atrial fibrillation.
4. If untreated, screen regularly for the development of overt hyperthyroidism (elevated free T_4 concentrations).

C. Thyroid Storm
   1. Severe and life-threatening decompensated thyrotoxicosis. Mortality rate may be as high as 20%.
   2. Precipitating causes: Trauma, infection, antithyroid agent withdrawal, severe thyroiditis, postablative therapy (especially if inadequate pretreatment)
   3. Presentation: Fever, tachycardia, vomiting, dehydration, coma, tachypnea, delirium
   4. Pharmacotherapy
      a. Propylthiouracil
         i. 500- to 1000-mg loading dose; then 250 mg every 4 hours
         ii. Blocks new hormone synthesis
         iii. Can use methimazole 60–80 mg daily
      b. Iodide therapy 1 hour after propylthiouracil initiation (dosed as stated earlier) to block hormone release
      c. β-Blocker therapy: Propranolol or esmolol commonly used to control symptoms and block conversion of T_4 to T_3 in high doses
      d. Acetaminophen as antipyretic therapy, if needed (avoid nonsteroidal anti-inflammatory drugs because of displacement of protein-bound thyroid hormones)
      e. Corticosteroid therapy: Hydrocortisone 300-mg intravenous loading dose; then 100 mg every 8 hours (or equivalent dosages of, for example, dexamethasone, prednisolone). Provides prophylaxis against relative adrenal insufficiency and can block conversion of T_4 to T_3

Patient Case

2. A 63-year-old woman has Hashimoto disease. Her thyroid laboratory values today include TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and free T_4 0.5 ng/dL (normal 0.8–1.9 ng/dL). She feels consistently rundown and has dry skin that does not respond to the use of hand creams. Which is the best drug for initial treatment of her condition?

   A. Levothyroxine.

   B. Liothyronine.

   C. Desiccated thyroid.

   D. Methimazole.

D. Hypothyroid Disorders
   1. Classification
      a. Hashimoto disease: Most common hypothyroid disorder in areas with iodine sufficiency
         i. Autoimmune-induced thyroid injury resulting in decreased thyroid secretion
         ii. Disproportionately affects women
      b. Iatrogenic: Thyroid resection or radioiodine ablative therapy for hyperthyroidism
      c. Iodine deficiency most common cause worldwide
      d. Secondary causes
         i. Pituitary insufficiency (failure to produce adequate TSH secretion, called by some a central or secondary hypothyroidism)
         ii. Drug induced (e.g., amiodarone, lithium)
   2. Diagnosis
      a. Low free T_4 serum concentrations
      b. Elevated TSH concentrations, typically seen as first laboratory abnormality, usually greater than 10 mIU/L (normal or low if central hypothyroidism is the cause)
      c. Thyroid antibodies such as antithyroid peroxidase and antithyroglobulin autoantibodies
      d. Screen patients older than 60, especially women (many different screening recommendations are given by various professional groups with little consensus).

3. Clinical presentation
    a. Cold intolerance
    b. Dry skin
    c. Fatigue, lethargy, weakness
    d. Weight gain
    e. Bradycardia
    f. Slow reflexes
    g. Coarse skin and hair
    h. Periorbital swelling
    i. Menstrual disturbances (more frequent or longer menstruation, painful menstruation, menorrhagia) caused by hypometabolism of estrogen
    j. Goiter (primary hypothyroidism)
4. Therapy goals
    a. Minimize or eliminate symptoms; improve quality of life
    b. Minimize long-term damage to organs (myxedema coma, heart disease)
    c. Normalize free T_4 and TSH concentrations
5. Therapeutics
    a. Levothyroxine (drug of choice)
        i. Mechanism of action: Synthetic T_4
        ii. Dosing
            (a) Initial
                (1) In otherwise healthy adults, 1.6 mcg/kg (use ideal body weight) per day
                (2) In patients age 50–60, consider 50 mcg/day.
                (3) In those with existing cardiovascular disease, consider 12.5–25 mcg/day.
            (b) For optimal bioavailability, usually dosed in the morning on an empty stomach 30–60 minutes before breakfast or at bedtime 3–4 hours after last meal; dosed separately from other medications (particularly calcium or iron supplements and antacids)
            (c) Dosage titration depending on response (control of symptoms, normalization of TSH and free T_4)
            (d) Can increase or decrease in 12.5- to 25-mcg/day increments, or consider increase or decrease in 10%–15% of weekly dose
            (e) Daily requirements are higher in pregnancy (separate guidelines available for treating thyroid disorders in pregnancy).
            (f) For hospitalized patients already receiving levothyroxine but for whom oral administration not an option, the intravenous dose is 75% of the oral dose.
        iii. Monitoring
            (a) 4–8 weeks is appropriate to assess patient response in TSH after initiating or changing therapy (about a 7-day half-life for T_4). May take longer for TSH to achieve steady-state concentrations
            (b) Use free T_4 rather than TSH if central or secondary hypothyroidism; obtain sample before daily dosing of levothyroxine
        iv. Adverse effects
            (a) Hyperthyroidism
            (b) Cardiac abnormalities (tachyarrhythmias, angina, myocardial infarction)
            (c) Linked to risk of fractures (usually at higher dosages or over-supplementation)
        v. Efficacy: If levothyroxine is properly dosed, most patients will maintain TSH and free T_4 in the normal ranges and experience symptomatic relief.
        vi. Considered drug of choice because of its adverse effect profile, cost, lack of antigenicity, and uniform potency

vii. Bioequivalence
(a) Guidelines recommend brand-name levothyroxine or consistent use of specific generic product.
(b) TSH concentrations in bioequivalence testing were never obtained; small changes in T_4 between products can significantly change the TSH. Pharmacokinetic studies were conducted in healthy subjects with normal thyroid function.

b. Liothyronine (synthetic T_3), liotrix (synthetic T_4/T_3), and desiccated thyroid are not recommended by leading professional organizations or clinical guidelines. If converting from dessicated thyroid preparation to levothyroxine, 60 mg of dessicated thyroid is about equal to 100 mcg of levothyroxine.

E. Subclinical Hypothyroidism
1. Definition: Elevated TSH (above upper limit of reference range) with normal T_4. Often the result of early Hashimoto disease
2. Risk
a. TSH greater than 7 mIU/L in older adults associated with elevated risk of heart failure
b. TSH greater than 10 mIU/L associated with elevated risk of coronary heart disease
3. Treatment of subclinical hypothyroidism is controversial because benefits in identified patients are inconclusive. An association between the use of levothyroxine and a reduction in heart disease in younger patients (40–70 years of age) does appear to exist, but not in older patients (older than 70).
4. Whom to treat
a. TSH 10 mIU/L or greater
b. TSH 4.5–10 mIU/L and
i. Symptoms of hypothyroidism
ii. Antithyroid peroxidase antibodies present
iii. History of cardiovascular disease, heart failure, or risk factors for such
c. Initial daily doses of 25–75 mcg of levothyroxine recommended
5. If untreated, screen regularly for the development of overt hypothyroidism (decreased free T_4 concentrations).

F. Myxedema Coma
1. Severe and life-threatening decompensated hypothyroidism; mortality rate 30%–60%
2. Precipitating causes: Trauma, infections, heart failure, medications (e.g., sedatives, narcotics, anesthesia, lithium, amiodarone)
3. Presentation: Coma is not required and is uncommon, despite terminology; altered mental state (very common); diastolic hypertension; hypothermia; hypoventilation
4. Pharmacotherapy
a. Intravenous thyroid hormone replacement
i. T_4: 200- to 400-mcg intravenous loading dose, followed by 1.6 mcg/kg daily. Lower the initial dose in frail patients or patients with established cardiovascular disease. Intravenous doses are around 75% of oral administration.
ii. Some advocate the use of T_3 over T_4, given that T_3 is more biologically active and that T_4/T_3 conversion may be suppressed in myxedema coma. Cost and availability limit intravenous T_3 use.
b. Antibiotic therapy: Given common infectious causes, some clinicians advocate empiric therapy with broad-spectrum antibiotics.

c. Corticosteroid therapy
   i. Hydrocortisone 100 mg every 8 hours (or equivalent steroid) or doses appropriate for the stressed state
   ii. Can be discontinued if random cortisol concentration not depressed
d. Adjust levothyroxine dose on the basis of serum T_3 measured every 1 or 2 days.

II. PITUITARY GLAND DISORDERS

Table 1. Basic Pituitary Gland (Anterior) Hormone Physiology

Anterior Pituitary Hormone	Primary Function(s)	Hypothalamic Stimulator	Primary Secretion Inhibitor
Growth hormone (GH)	Promote tissue growth	GH-releasing hormone	Somatostatin Insulin-like growth factor-1
Adrenocorticotropic hormone (ACTH)	Stimulate adrenal cortisol and androgen release	Corticotropin-releasing hormone	Cortisol
Thyroid-stimulating hormone (TSH)	Metabolic stability	Thyrotropin-releasing hormone	Triiodothyronine
Prolactin	Regulate lactation	Thyrotropin-releasing hormone	Dopamine
Follicle-stimulating hormone	Maturation of ovarian follicles Sperm production	Gonadotropin-releasing hormone	Inhibin Estrogens
Luteinizing hormone	Secretion of sex steroids	Gonadotropin-releasing hormone	Estrogens and progestins Testosterone

A. Classification (focus on the common anterior pituitary disorders)
   1. Hypersecretory diseases
      a. Acromegaly and gigantism: Usually caused by growth hormone (GH)-secreting pituitary adenoma
      b. Hyperprolactinemia
         i. Most common cause is prolactinomas (prolactin-secreting pituitary tumor).
         ii. Drug induced (e.g., serotonin reuptake inhibitors and some antipsychotics)
         iii. Central nervous system lesions
   2. Hyposecretory disease
      a. GH deficiency
         i. Congenital abnormality caused by GH gene deletion, GH-releasing hormone deficiency
         ii. Other causes are pituitary aplasia, head trauma, and central nervous system infection.
         iii. Idiopathic
      b. Panhypopituitarism: Result of partial or complete loss of anterior and posterior pituitary function. Can be caused by primary pituitary tumor, ischemic necrosis of the pituitary, trauma from surgery, or irradiation. Results in adrenocorticotropic hormone (ACTH) deficiency, GH deficiency, hypothyroidism, gonadotropin deficiency

B. Acromegaly
   1. Diagnosis and clinical presentation
      a. Failure of an oral glucose tolerance test (OGTT) to suppress GH serum concentrations but with elevated IGF-1 (GH serum concentrations alone are unreliable, given the pulsatile pattern of release in the body.)

b. Clinical presentation (Note that the disease has a slow onset, and many symptoms do not appear for years.)
    i. Excessive sweating
    ii. Osteoarthritis, joint pain, paresthesias, or neuropathies
    iii. Coarsening of facial features
    iv. Increased hand volume or ring size, increased shoe size
    v. Hypertension, heart disease, cardiomyopathy
    vi. Sleep apnea
    vii. T2D

2. Therapy goals
    a. Reduce GH and IGF-1 concentrations
    b. Decrease mortality
    c. Improve clinical symptoms
    d. Normalize IGF-1 concentrations and suppressed GH concentrations after OGTT
3. Therapeutics
    a. Treatment of choice is surgical resection of tumor, if causative.
    b. Pharmacotherapy usually reserved for:
        i. Control before surgery or irradiation
        ii. When surgery is not possible (usually requires lifelong pharmacotherapy)
        iii. Surgical failures or relapses after period of remission after surgery
    c. Dopamine agonists (e.g., bromocriptine, cabergoline)
        i. Mechanism of action: Dopamine agonist that, in acromegaly, causes paradoxical decrease in GH production
        ii. Dosing (bromocriptine is most commonly used agent)
            (a) Initial: 1.25 mg/day by mouth
            (b) Maximal: 20–30 mg/day (can titrate once or twice weekly, as needed)
        iii. Adverse effects
            (a) Fatigue, dizziness, nervousness
            (b) Diarrhea, abdominal pain
        iv. Efficacy: Normalization of IGF-1 concentrations in about 10% of patients. More than 50% of patients experience symptomatic relief.
    d. Somatostatin analog (e.g., octreotide)
        i. Mechanism of action: Blocks GH secretion; 40 times more potent than endogenous somatostatin
        ii. Dosing
            (a) Initial: 50–100 mcg subcutaneously every 8 hours or 20 mg orally twice daily (Oral use is typically reserved for patients who require long-term maintenance and have responded to injectable octreotide)
            (b) Maximal: Little benefit greater than 600 mcg/day or 80 mg daily with oral administration
            (c) If response is adequate, can be changed to long-acting octreotide formulation administered once monthly
            (d) Orally with a glass of water on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal
        iii. Adverse effects
            (a) Diarrhea, nausea, cramps, flatulence, fat malabsorption
            (b) Arrhythmias
            (c) Hypothyroidism
            (d) Biliary tract disorders
            (e) Changes in serum glucose concentrations (usually reduces)

iv. Efficacy: 50%–60% of patients experience normalization of IGF-1 concentrations with good symptomatic relief as well. May shrink tumor mass in some patients

e. GH receptor antagonist (e.g., pegvisomant)
   i. Mechanism of action: GH derivative binds to liver GH receptors and inhibits IGF-1
   ii. Dosing
      (a) Initial: 40 mg once-daily subcutaneous injection loading dose and then 10 mg once daily
      (b) Maximal: 30 mg/day
   iii. Adverse effects
      (a) Nausea, vomiting
      (b) Flulike symptoms
      (c) Reversible elevations in hepatic transaminase
   iv. Efficacy: More than 95% of patients attain normal IGF-1 concentrations, and most have improved symptoms.

Patient Case

3. A 28-year-old woman presents with acne, facial hair growth, and irregular menses that have lasted for 6–7 months. Her medical history includes hypertension and depression. Her pituitary and thyroid tests results have been negative. Her current medications include amlodipine and fluoxetine. Her prolactin concentration today is 112 ng/mL (normal 15–25 ng/mL). Which is the most likely cause of her elevated prolactin concentration?

   A. Amlodipine.

   B. Prolactin-secreting adenoma.

   C. Pregnancy.

   D. Fluoxetine.

C. Hyperprolactinemia
   1. Causes
      a. Direct: Pituitary tumor (lactotroph adenoma = prolactinoma accounting for around 40% of tumors)
      b. Indirect: Drug induced (most common nontumor cause), renal failure, hypothyroidism, breastfeeding
      c. Potential causative drugs: Typical antipsychotics, opiates, non-dihydropyridine calcium channel blockers, antidepressants
   2. Diagnosis and clinical presentation
      a. Elevated serum prolactin concentrations; may be challenging to find specific cause (unless drug induced)
      b. Clinical presentation
         i. Amenorrhea, anovulation, infertility, hirsutism, and acne in women
         ii. Erectile dysfunction, decreased libido, gynecomastia, and reduced muscle mass in men
         iii. Headache, visual disturbances, bone loss
   3. Therapy goals
      a. Normalize prolactin concentrations
      b. Normalize gonadotropin secretion
      c. Relieve symptoms
      d. Decrease tumor size
   4. Therapeutics
      a. Surgical resection of tumor, if tumor is very large, causes severe compression of adjacent tissues, or patient does not respond to pharmacotherapy

b. Discontinue causative agent if drug induced.
    i. Recheck prolactin concentration 3 days after discontinuation.
    ii. Select agent with similar action but no known effect on prolactin concentrations.
    iii. If discontinuation of causative agent not feasible, consider dopamine agonist
c. Dopamine agonists (preferred to surgery in most cases)
    i. Cabergoline (preferred agent according to the Endocrine Society guidelines, long-acting oral agent; adverse effect profile similar to that for bromocriptine but fewer gastrointestinal [GI] adverse effects)
        (a) Initial: 0.5 mg once weekly
        (b) Maximal: 4.5 mg/week
    ii. Bromocriptine (see previous text)
    iii. Efficacy: May restore fertility in more than 90% of women. Long-term cure rates are around 60% for smaller tumors, around 25% for larger tumors. Cabergoline may be easier for patients to take, given its weekly administration.
    iv. Consider tapering or discontinuing after 2 years of therapy if asymptomatic, prolactin concentrations normalized, and no tumor remnant by imagery

D. GH Deficiency:
1. Diagnosis and clinical presentation
    a. Decreased GH concentrations after provocative pharmacologic challenge (e.g., insulin, clonidine, GH-releasing hormone)
    b. Clinical presentation
        i. Delayed growth velocity or short stature
        ii. Central obesity
        iii. Immaturity of the face or prominence of the forehead
2. Therapy goals
    a. Increase growth velocity
    b. Increase final adult height when treating children
3. Therapeutics: Recombinant GH (somatropin)
    a. Dosing
        i. Depends on which of the various products are selected (dosed subcutaneously or intramuscularly once daily)
        ii. When to discontinue therapy on the basis of growth velocity is controversial.
        iii. Once- or twice-monthly long-acting depot formulation is also available.
    b. Adverse effects
        i. Arthralgia, injection-site pain
        ii. Rare but serious cases of idiopathic intracranial hypertension have been reported.
    c. Efficacy: All products are considered equally efficacious.

III. ADRENAL GLAND DISORDERS

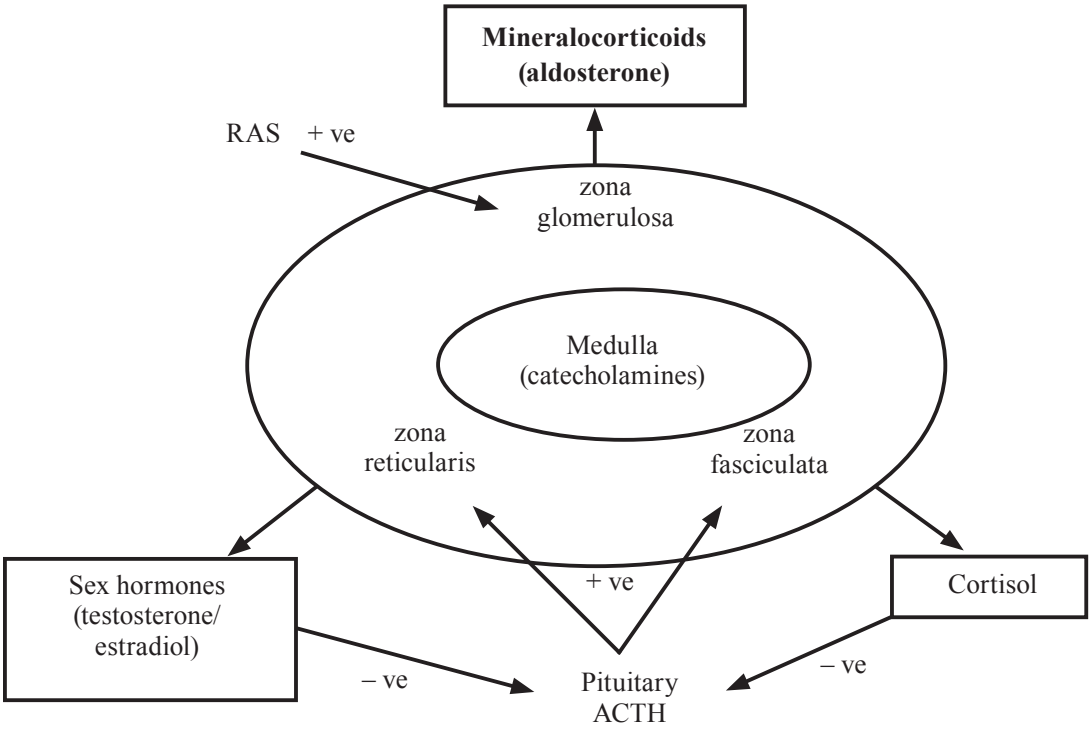

Figure 2. Basic adrenal cortex hormone physiology.
ACTH = adrenocorticotropic hormone; RAS = renin-angiotensin system; +ve = positive stimulation; –ve = negative feedback.

Patient Case

4. A 44-year-old man has consistently high blood pressure (172/98 mm Hg today), despite his documented adherence to two maximal-dose blood pressure medications. He has frequent headaches, increased thirst, and fatigue. His urine free cortisol is 45 mcg/24 hours (normal range 20–90) and plasma aldosterone/renin ratio is 125 (normal is less than 25). Which most likely caused this patient's uncontrolled hypertension?

   A. Cushing syndrome.

   B. Addison disease.

   C. Hyperprolactinemia.

   D. Hyperaldosteronism.

A. Hypersecretory Cortisol Diseases (Cushing syndrome)

1. Classification
   a. ACTH-dependent: Result of excessive ACTH secretion
      i. Pituitary corticotroph adenoma (Cushing disease)
      ii. Ectopic ACTH syndrome (extrapituitary tumor)
   b. ACTH-independent: Result of excessive cortisol secretion or exogenous steroids
      i. Unilateral adrenocortical tumors
      ii. Bilateral adrenal hyperplasia or dysplasia
      iii. Exogenous steroid administration

2. Diagnosis and clinical presentation
    a. Presence of hypercortisolism through 24-hour urinary free cortisol concentration
    b. Differentiate etiology (key to treatment options).
        i. Plasma ACTH concentrations (normal or elevated in ACTH-dependent)
        ii. Pituitary magnetic resonance imaging (Cushing syndrome vs. ectopic ACTH syndrome)
        iii. Overnight dexamethasone suppression test
        iv. Late-night salivary cortisol concentration
        v. 24-hour urinary free cortisol (low sensitivity)
    c. Clinical presentation
        i. Central obesity and facial rounding quite common
        ii. Peripheral obesity and fat accumulation
        iii. Myopathies
        iv. Osteoporosis, back pain, compression fracture
        v. Abnormal glucose tolerance or diabetes
        vi. Amenorrhea and hirsutism in women
        vii. Lower abdominal pigmented striae (red to purple)
        viii. Hypertension (principal cause of morbidity and mortality)
3. Therapy goals
    a. Reduce morbidity and mortality and eliminate cause
    b. Reverse clinical features
    c. Normalize biochemical changes (when possible)
    d. Achieve long-term control without recurrence (remission when possible)
4. Therapeutics
    a. If excessive exogenous corticosteroid use is causative, discontinue or minimize use.
    b. Surgical resection of causative area or tumor is usual treatment of choice.
    c. Pharmacotherapy is usually reserved on the basis of the same criteria listed earlier for pituitary adenomas.
    d. Efficacy is measured by control of symptoms and normalization of 24-hour urine-free cortisol concentrations.
    e. Glucocorticoid replacement may be necessary if circulating cortisol is reduced to lower than physiologic concentrations.
    f. Inhibit ACTH secretion
        i. Pasireotide
            (a) Mechanism of action: Somatostatin analog blocks ACTH secretion from pituitary, leading to decreased circulating cortisol concentrations (better selectivity to pertinent somatostatin receptors than other analogs such as octreotide). Usually not effective for adrenally caused Cushing syndrome.
            (b) Dosing: 0.6–0.9 mg twice-daily subcutaneous injection (dose adjustments based on urinary free cortisol and symptom improvements). Also available in a once-monthly intramuscular formulation.
            (c) Adverse effects: Hyperglycemia, hypocorticalism, diarrhea, nausea, gallstones, headache, bradycardia
            (d) Obtain an electrocardiogram, FPG, A1C, liver function tests, and gallbladder ultrasonography before initiating therapy.
            (e) Self-monitor BG values every week for first 2–3 months, and then periodically obtain liver function tests 1–2 weeks after starting therapy; then obtain them monthly for 2–3 months and then every 6 months. Repeat gallbladder ultrasonography at 6- to 12-month intervals.
        ii. Cabergoline (see dosing and ADR profile listed earlier)

g. Inhibit cortisol synthesis
   i. Osilodrostat
      (a) Mechanism of action: Hinders cortisol production by blocking the 11-β-hydroxylase enzyme
      (b) Dosing
         (1) Initial: 2 mg twice daily by mouth
         (2) Maximal: 30 mg twice daily
      (c) Adverse effects
         (1) Headache
         (2) Nausea/vomiting
         (3) Fatigue
         (4) QT prolongation (obtain baseline electrocardiogram 1 week after initiating therapy)
   ii. Ketoconazole
      (a) Mechanism of action: In addition to its antifungal activity, it hinders cortisol production by inhibiting 11β- and 17α-hydroxylase.
      (b) Dosing
         (1) Initial: 200 mg twice daily by mouth
         (2) Maximal: 400 mg three times daily
      (c) Adverse effects
         (1) Gynecomastia
         (2) Abdominal discomfort
         (3) Reversible hepatic transaminase elevations
         (4) Be aware of potential drug-drug interactions; inhibits CYP3A4 (strong), P-glycoprotein/ABCB1.
   iii. Mitotane
      (a) Mechanism of action: Inhibits 11β-hydroxylase but also has some direct adrenolytic activity
      (b) Dosing
         (1) Initial: 500–1000 mg/day by mouth (some use much higher daily dosages, but they are not well tolerated)
         (2) Maximal: 9–12 g/day
      (c) Adverse effects
         (1) Adrenocortical atrophy: Can persist on discontinuation and, in severe cases, may necessitate androgen and glucocorticoid replacement
         (2) Anorexia
         (3) Ataxia
         (4) Abdominal discomfort
         (5) Lethargy
   iv. Etomidate
      (a) Mechanism of action: Similar to ketoconazole, inhibits 11β-hydroxylase
      (b) Dosing
         (1) Initial: 0.03 mg/kg intravenously, followed by a 0.1-mg/kg/hour infusion
         (2) Maximal: 0.3 mg/kg/hour
      (c) Adverse effects
         (1) Pain at injection site
         (2) Nausea and vomiting
         (3) Myoclonus
         (4) Psychoses
      (d) Given route of administration is usually reserved for when rapid control of cortisol concentrations is needed and oral therapy is problematic.

v. Metyrapone (by compassionate use only)
(a) Mechanism of action: Hinders secretion of cortisol by blocking final step in cortisol synthesis by inhibiting 11β-hydroxylase activity
(b) Dosing
(1) Initial: 500 mg three times daily by mouth
(2) Average dose in Cushing syndrome is 2000 mg/day, but dose is about 4000 mg in ectopic ACTH syndrome.
(c) Adverse effects
(1) Hypoadrenalism
(2) Hypertension
(3) Worsening of hirsutism and acne if present before treatment
(4) Headache
(5) Abdominal discomfort

h. Mifepristone for hyperglycemia associated with endogenous Cushing syndrome; proposed to limit binding of cortisol; can reduce insulin requirements and improve clinical symptoms associated with hyperglycemia

B. Hyperaldosteronism: Primary Aldosteronism
1. Classification
a. Bilateral adrenal hyperplasia (70% of cases)
b. Aldosterone-producing adenoma (30% of cases)
2. Diagnosis and clinical presentation
a. Elevated plasma aldosterone/renin ratio (normal ratio is less than 25)
b. Other features: Hypernatremia, hypokalemia, hypomagnesemia, glucose intolerance
c. Clinical presentation (can be asymptomatic)
i. Hypertension
ii. Muscle weakness or fatigue
iii. Headache
iv. Polydipsia
v. Nocturnal polyuria
3. Therapy goals (same as earlier for Cushing syndrome)
4. Therapeutics
a. Spironolactone (drug of choice)
i. Mechanism of action: mineralocorticoid receptor antagonist
ii. Dosing
(a) Initial: 25–50 mg/day by mouth
(b) Maximal: 400 mg/day
iii. Adverse effects
(a) Hyperkalemia
(b) Gynecomastia
(c) Abdominal discomfort
b. Eplerenone and amiloride are alternatives to spironolactone.

C. Hyposecretory Adrenal Disorders
1. Classification
a. Primary adrenal insufficiency (i.e., Addison disease)
i. Caused by autoimmune disorder, infection, or infarction
ii. Results in cortisol, aldosterone, and androgen deficiencies

   b. Secondary adrenal insufficiency
      i. Exogenous steroid use (from chronic suppression); oral, inhaled, intranasal, and topical administration
      ii. Surgery, trauma, infection, infarction
      iii. Results in impaired androgen and cortisol production
2. Diagnosis and clinical presentation (focus on Addison disease)
   a. Abnormal rapid cosyntropin (synthetic ACTH) stimulation test (blunted increase in cortisol concentrations) suggests adrenal insufficiency
   b. Clinical presentation
      i. Hyperpigmentation (caused by elevated ACTH concentrations)
      ii. Weight loss
      iii. Dehydration
      iv. Hyponatremia, hyperkalemia, elevated blood urea nitrogen
3. Therapy goals (same as earlier for Cushing syndrome)
4. Therapeutics (Table 2)
   a. Steroid replacement (replace cortisol loss)
      i. Oral administration is commonly dosed to mimic normal cortisol production circadian rhythm.
      ii. Two-thirds administered in the morning and one-third in the evening
         (a) This may cause periods of transient adrenal insufficiency or variable serum concentrations in some patients.
         (b) Daily cortisol production in average patient: 5–10 mg/m^2
   b. Hydrocortisone: 15 mg/day (use may reduce need for fludrocortisone compared with use of cortisone or prednisone)
      i. Cortisone acetate: 20 mg/day
      ii. Prednisone: 2.5 mg/day
      iii. Dexamethasone: 0.25–0.75 mg/day
   c. Fludrocortisone (replaces loss of mineralocorticoid): 0.05–0.2 mg/day by mouth
   d. For women with decreased libido or low energy levels because of androgen deficiency, dehydroepiandrosterone: 25–50 mg/day
   e. Efficacy can be measured by symptom improvement.
   f. Note that during times of stress or illness, corticosteroid dosages must be increased. Dose and route of administration depend on level of stress to the body.

Table 2. Comparative Glucocorticoid Dosing

Glucocorticosteroid	Relative Equivalent Dosing (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75

IV. OBESITY

A. Guidelines
   1. American College of Cardiology/American Heart Association (ACC/AHA) and The Obesity Society 2013 guidelines. Most of the therapeutic agents that follow were approved for obesity after the guideline was initiated and are not included.
   2. Endocrine Society 2015 guidelines are focused on new obesity agents. No specific recommendations of a particular agent over another, but a good review of the therapeutic options
   3. AACE/American College of Endocrinology 2016 guidelines. A comprehensive review of nonpharmacologic and pharmacologic therapy for obesity. Like the Endocrine Society guidelines, there are no specific recommendations regarding one agent over another.

B. Classification
   1. Based on BMI
   2. Normal: BMI 18.5–24.9 kg/m^2
   3. Overweight: BMI 25.0–29.9 kg/m^2
   4. Obesity
      a. Class I: BMI 30.0–34.9 kg/m^2
      b. Class II: BMI 35.0–39.9 kg/m^2
      c. Class III: BMI 40 kg/m^2 or greater

C. Therapy Goals
   1. Weight loss: Initial goal: 5%–10% decrease from baseline weight over 6 months
   2. Maintain lower weight in the long term
   3. Limit weight-induced comorbidities (e.g., T2D, hypertension, cardiovascular disease)

D. Nonpharmacologic Therapy (aimed at providing an energy deficit)
   1. Increased physical activity: 200–300 minutes per week (minimum 150)
   2. Dietary options: Any diet that has proven weight reduction data available is appropriate. No specific recommendations of one diet over another. Individualize according to patient preferences.
      a. Strive for at least a 500-kcal/day deficit.
      b. 1200–1500 kcal/day for women
      c. 1500–1800 kcal/day for men
   3. Behavioral intervention: According to ACC/AHA/The Obesity Society guidelines: Preferably in-person, high-intensity (at least 14 sessions in 6 months) comprehensive weight-loss intervention through group or individual sessions with a professional (e.g., dietitian, exercise specialist, health counselor)
   4. Surgery: Usually reserved for patients with class III obesity (BMI greater than 40 kg/m^2) or BMI of at least 35 kg/m^2 with at least one obesity-related comorbidity such as diabetes, hypertension, or obstructive sleep apnea
      a. Roux-en-Y gastric bypass (decreasing in frequency)
      b. Sleeve gastrectomy (now the most common surgery)
      c. Adjustable gastric banding
   5. Gastric balloons and transpyloric shuttle available for weight loss, Plenity (cellulose/citric acid) available for weight management

Patient Case

5. A patient takes the maximal daily dose of phentermine/topiramate for the treatment of obesity. The patient's baseline BMI is 36 kg/m^2 and weight is 115.7 kg (255 lb). Which best represents the minimum weight loss required to consider continuing treatment with this agent after 3 months of therapy?

   A. 3.2 kg (7 lb).

   B. 5.9 kg (13 lb).

   C. 7.7 kg (17 lb).

   D. 11.8 kg (26 lb).

E. Pharmacotherapy
   1. Always in conjunction with diet, physical activity, and behavioral therapy
   2. Medications should be reserved for those not achieving or sustaining weight reduction with adequate lifestyle modifications, in those with obesity, or in those with a BMI of at least 27 kg/m^2 with significant weight-related comorbidities (e.g., diabetes, hypertension, dyslipidemia).
   3. Medication selected according to risk-benefit profile should be approved by the U.S. Food and Drug Administration (FDA). After 1 year, approved agents should provide at least a statistically significant 5% weight loss difference from placebo, or at least 35% of treated subjects should achieve at least a 5% weight loss from baseline and twice that of placebo-treated subjects.
   4. Orlistat
      a. Mechanism of action: Reduced absorption of fat by inhibition of gastric and pancreatic lipases
      b. Dosing
         i. Prescription: 120 mg three times daily during or up to 1 hour after meals
         ii. Over the counter: 60 mg three times daily during or up to 1 hour after meals
      c. Adverse effects
         i. GI tract: Flatulence, oily stools, loose stools, fecal urgency, or incontinence (highly dependent on fat content of meal)
         ii. Reduced absorption of fat-soluble vitamins (A, D, E, and K): Use vitamin supplement before or well after use.
         iii. Hepatotoxicity, kidney stones (FDA warnings)
   5. Phentermine/extended-release topiramate (schedule IV)
      a. Mechanism of action: Phentermine promotes appetite suppression and decreases food intake secondary to its sympathomimetic activity. Mechanism of topiramate is unknown, but it can cause appetite suppression and satiety through increased γ-aminobutyrate activity.
      b. Dosing (phentermine/topiramate): Should be taken in the morning to avoid insomnia
         i. Initial: 3.75/23 mg daily for 2 weeks; then increase to 7.5/46 mg daily
         ii. If at least a 3% weight loss not achieved after 12 weeks, can discontinue or increase to 11.25/69 mg daily for 2 weeks; then increase to 15/92 mg daily, if tolerated
         iii. If at least a 5% weight loss not achieved with 15/92 mg daily, discontinue use. Taper when discontinuing to avoid seizures.
         iv. Dosing in moderate hepatic or renal impairment: Do not exceed 7.5/46 mg daily.
      c. Adverse effects: Dry mouth, paresthesia, constipation, dysgeusia, insomnia, attention and memory disturbances, increased heart rate
      d. In women of childbearing age, obtain a negative pregnancy test before initiating and monthly thereafter because of fetal toxicity. Stress the importance of adequate contraception during use.
      e. Discontinue use if patient does not achieve at least a 5% weight loss after 12 weeks of use.

6. Bupropion/naltrexone
    a. Mechanism of action: Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)
    b. Dosing (8 mg naltrexone/90 mg bupropion tablets extended release)
        i. Dosage escalation at weekly intervals by 1 tablet daily
        ii. Initially, 1 tablet once daily
        iii. Target dosage: 2 tablets twice daily
    c. Adverse effects: Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth
    d. Precautions and contraindications: Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal. Avoid with chronic use of opioids.
    e. Discontinue use if at least a 5% weight loss is not achieved after 12 weeks of use.
7. Liraglutide
    a. Mechanism of action: Glucagon-like peptide-1 (GLP-1) agonist (part of incretin system). Thought to cause satiety and delay gastric emptying. Used in treatment of T2D (see text that follows)
    b. Dosing (administered subcutaneously by pen device)
        i. Target dosage higher in obesity than in treatment of diabetes. Brand-name product for obesity is not approved for diabetes and vice versa.
        ii. Initially, 0.6 mg once daily; increase by 0.6 mg at weekly intervals
        iii. Target dosage for obesity: 3 mg daily
    c. Adverse effects: Nausea, vomiting, diarrhea, constipation, dyspepsia
    d. Precautions and contraindications
        i. See the Diabetes Mellitus section.
        ii. Do not use with other GLP-1 agonists used in the treatment of diabetes mellitus (DM).
    e. Discontinue use if the patient does not achieve at least a 4% weight loss after 16 weeks of therapy or if the patient cannot tolerate the target 3-mg daily dosage.
8. Semaglutide
    a. Mechanism of action similar to liraglutide
    b. Dosing (administered subcutaneously by pen device)
        i. Target dose, like liraglutide, is higher than in the treatment of diabetes and the brand name is also different.
        ii. Initially, 0.25 mg once weekly, increased at monthly intervals
        iii. Target dose for obesity: 2.4 mg once weekly
    c. Adverse effects, precautions, contraindications: Similar to liraglutide
    d. Discontinue if patient cannot tolerate the target dose.
9. Tirzepatide does not yet have FDA approval for weight loss but seems likely based on recent data published in the *New England Journal of Medicine*.
10. Diethylpropion (schedule IV), phentermine (schedule IV), phendimetrazine (schedule III)
    a. Should be used only for a limited time, up to 3 months, and avoid in those with abuse potential
    b. Clinical guidelines do not recommend their use.
    c. Adverse effects: Increased blood pressure, constipation, increased heart rate, dysrhythmias, abuse potential (avoid in patients with hypertension or a history of cardiovascular disease)
11. Other issues
    a. Concurrent use of obesity medications has not been studied.
    b. Comparative studies between agents are lacking (although liraglutide appears more effective at weight loss compared to orlistat, and semaglutide is more effective compared to liraglutide).
    c. Long-term safety of all agents is unknown.
    d. Consider obesity a chronic condition. Weight gain after discontinuation of agent is likely
12. Off-label medications used but not well studied specifically for obesity: Selective serotonin reuptake inhibitors, zonisamide, metformin, pramlintide
13. Lorcaserin was removed from the market in early 2020 after increased risk of some cancers was detected.

V. POLYCYSTIC OVARY SYNDROME

A. Background and Classification
   1. Can be a cause of infertility in up to 20% of infertile couples
   2. Mainly considered to be caused by androgen excess or hyperandrogenism
   3. Underlying cause appears to be insulin resistance (in patients with and without obesity), with subsequent compensatory insulin hypersecretion or increased insulin action. This increased action stimulates androgen secretion by the ovaries or adrenal cells, leading to increased luteinizing hormone (LH) secretion but normal or low follicle-stimulating hormone (FSH) concentrations, with a subsequent decrease in follicular maturation and anovulation.
   4. Has several potential comorbidities with endocrine and cardiovascular implications (e.g., T2D, obesity)
   5. Can affect 6%–10% of women (or more depending on diagnostic criteria used), making it one of the most prevalent endocrine disorders in young women
   6. Women younger than 50 are at higher cardiovascular disease risk.

B. Diagnosis
   1. Still somewhat under debate; no clear consensus
   2. 1990 National Institutes of Health criteria
      a. Hyperandrogenism or hyperandrogenemia
      b. Oligo-ovulation (infrequent or irregular ovulation)
      c. Exclusion of other secondary causes, particularly adrenal hyperplasia, Cushing syndrome, hyperprolactinemia
   3. 2003 Rotterdam criteria: Presence of at least two of the following and ruling out secondary causes
      a. Menstrual irregularity (oligo-ovulation or anovulation)
      b. Hyperandrogenism (clinical or biochemical signs)
      c. Polycystic ovaries (by transvaginal ultrasonography)
      d. Recommended by the Endocrine Society guideline
   4. 2006 Androgen Excess Society: Follow 1990 National Institutes of Health criteria, but recognize concerns brought about from the Rotterdam criteria.

C. Clinical Presentation
   1. Clinical signs of hyperandrogenism: Hirsutism, acne, pattern alopecia (can vary by ethnicity)
   2. Biochemical signs of hyperandrogenism (should not be used as the sole criterion because 20%–40% of patients with PCOS may be in the normal range)
      a. Elevated free or total serum testosterone
      b. LH/FSH ratio greater than 2
   3. Infrequent, irregular (e.g., late), or no ovulation, leading to irregular menses
   4. Infertility despite unprotected and frequent intercourse during the past year
   5. In patients with obesity (50%–80% of cases), prediabetes (impaired glucose tolerance) or T2D may be present.

D. Therapy Goals
   1. Normalize ovulation and menses
   2. Improve fertility in those who want to become pregnant
   3. Limit clinical signs
   4. Reduce progression to T2D (perhaps cardiovascular disease)

E. Nonpharmacologic Therapy
   1. Weight loss (5%–10%) important in patients who are overweight or have obesity
   2. Mechanical hair removal for hirsutism

F. Pharmacotherapy
   1. Fertility improvement
      a. Clomiphene citrate
         i. Mechanism of action: Induces ovulation as a selective estrogen receptor modulator that improves LH-FSH secretion
         ii. Dosing
            (a) 50 mg/day for 5 days starting on the third or fifth day of the menstrual cycle
            (b) Increase to 100 mg if ovulation does not occur after first cycle of treatment.
            (c) Maximal daily dosage: 150–200 mg/day
         iii. Adverse effects: Flushing, GI discomfort, vision disturbances, vaginal dryness, multiple pregnancies
         iv. Improved ovulation and pregnancy rates when used in combination with metformin
      b. Gonadotropin (e.g., recombinant FSH) or recombinant gonadotropin-releasing hormone therapy with or without clomiphene
         i. Mechanism of action: Normalizes LH/FSH ratio to stimulate ovulation
         ii. Dosing: Many dosing strategies used
         iii. Adverse effects: Multiple pregnancies, ovarian hypertrophy, miscarriage, mood swings, breast discomfort
      c. Letrozole
         i. Mechanism of action: Aromatase inhibitor prevents conversion of androgens to estrogen, which results in an increased secretion of FSH from the anterior pituitary; conflicting meta-analysis data on its effectiveness compared with clomiphene on pregnancy rates
         ii. Dosing: 2.5–5 mg daily
         iii. Adverse effects: Edema, sweating, constipation, nausea, arthralgias, headache
         iv. Considered the treatment of choice for ovulation induction by the American College of Obstetricians and Gynecologists in 2018 because of better live birth rates than with clomiphene
   2. Symptomatic improvement
      a. Hormonal contraceptives (estrogen/progestin combination): Endocrine Society first-line therapy for menstrual abnormalities, hirsutism, or acne
      b. Metformin
         i. Effective for metabolic and glycemic abnormalities, if present, but only modestly effective for hirsutism
         ii. Alternative to hormonal contraception for irregular menses when hormonal contraceptives are contraindicated
         iii. Few data to support use for increased fertility (may improve pregnancy rate but not shown to improve rates of live births)
      c. Spironolactone
         i. Often added to hormonal contraceptives
         ii. Can help with hirsutism
      d. Pioglitazone: Questionable whether benefits outweigh risks in PCOS. Not recommended in Endocrine Society guidelines

VI. DIABETES MELLITUS

A. Consensus Recommendations
   1. American Diabetes Association (ADA). Updated yearly in the January supplement of Diabetes Care (www.diabetes.org)
   2. American College of Endocrinology/AACE
   3. Canadian Diabetes Association
   4. Various European groups
   5. For the remainder of this section, unless otherwise noted, the ADA recommendations will be followed.

B. Classification
   1. T1D
      a. Attributable to cellular-mediated β-cell destruction leading to insulin deficiency (insulin needed for survival)
      b. Accounts for 5%–10% of DM
      c. Formerly known as *insulin-dependent diabetes* and *juvenile-onset diabetes*
      d. Usually presents in childhood or early adulthood but can present in any stage of life
      e. Usually symptomatic with a rapid onset in childhood, but a slower onset can occur in older adults
      f. The ADA now recommends a staging of patients with T1D based on the degree of dysglycemia and symptoms.
         i. Stage 1: Multiple autoantibodies present but glucose concentrations are normal
         ii. Stage 2: Multiple autoantibodies present, glucose concentrations consistent with prediabetes (see criteria in text that follows), and patient is asymptomatic
         iii. Stage 3: Symptomatic and glucose concentrations consistent with diabetes (see criteria in text that follows)
   2. T2D
      a. Results primarily from insulin resistance in muscle and liver, with subsequent defect in pancreatic insulin secretion, though GI, brain, liver, and kidneys are all involved in the pathophysiology
      b. Accounts for 90%–95% of diabetes mellitus
      c. Formerly known as *non–insulin-dependent diabetes* or *adult-onset diabetes*
      d. Often asymptomatic, with a slow onset over 5–10 years. Rationale for early, frequent screening of those at risk (see text that follows) and initial assessment for complications at diagnosis
      e. Increased trends in T2D in children and adolescents attributed to rise in obesity
   3. Maturity-onset diabetes of the young
      a. Result of genetic disorder leading to impaired secretion of insulin with little or no impairment in insulin action
      b. Onset usually before age 25 and can mimic T1D or T2D
      c. Often misdiagnosed for type 1 diabetes. Patients may respond to sulfonylurea therapy.
   4. Gestational diabetes
      a. Glucose intolerance occurring during pregnancy
      b. Prevalence: 1%–14% of pregnancies (complicates about 4% of pregnancies)
      c. Most common in third trimester
   5. Prediabetes
      a. Impaired glucose tolerance
      b. Impaired fasting glucose
   6. Other DM types
      a. Genetic defects in β-cell function or insulin action
      b. Diseases of the pancreas (e.g., pancreatitis, neoplasia, cystic fibrosis)
      c. Drug or chemical induced (e.g., glucocorticoids, nicotinic acid, protease inhibitors, atypical antipsychotics)

Patient Case

6. A 64-year-old African American woman has had a 12-kg (27 lb) weight increase during the past year, primarily because of inactivity and a poor diet. Her BMI is 44 kg/m^2. Her mother and sister both have T2D. Her fasting glucose concentration today is 212 mg/dL. Which is the best course of action?

   A. Diagnose T2D and begin treatment.

   B. Diagnose T1D and begin treatment.

   C. Obtain another glucose concentration today.

   D. Obtain an A1C today in addition to the glucose concentration.

C. Screening for DM (using glycemic diagnostic criteria discussed in greater detail in the text that follows)
   1. T1D
      a. Symptomatic patients
      b. Asymptomatic patients at higher risk
         i. First-degree relatives with T1D
         ii. Measure islet autoantibodies to assess risk of T1D.
         iii. If screen is positive for antibodies, counsel on symptoms of hyperglycemia and risk of DM. Consider enrollment in observational study.
   2. T2D
      a. Age 35 or older, repeat every 3 years if normal
      b. Screen regardless of age if BMI is 25 kg/m^2 or greater (23 kg/m^2 or greater in Asian Americans) and at least one of the following risk factors:
         i. History of cardiovascular disease
         ii. A1C is 5.7% or greater, impaired glucose tolerance, or impaired fasting glucose in previous testing
         iii. History of PCOS
         iv. HDL less than 35 mg/dL or TG greater than 250 mg/dL
         v. Hypertension
         vi. High-risk ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
         vii. First-degree relative with T2D
         viii. Physical inactivity
         ix. Insulin resistance conditions (e.g., severe obesity, acanthosis nigricans)
   3. Gestational DM
      a. Screen at first prenatal visit for undiagnosed T2D in all patients with T2D risk factors present.
      b. Screen at 24–28 weeks' gestation using OGTT.
      c. If a diagnosis of gestational DM is made, screen for diabetes 4–12 weeks after delivery.
      d. Continue to screen patients who have had gestational DM every 3 years for T2D for life.

D. DM Diagnosis
   1. T1D and T2D diagnosis
      a. Glycemic values in nonpregnant patients
         i. FPG
            (a) Easy, convenient
            (b) 126 mg/dL or greater
         ii. Random plasma glucose
            (a) 200 mg/dL or greater with symptoms of hyperglycemia
            (b) Common hyperglycemia symptoms include polyuria, polydipsia, and unexplained weight loss.

iii. OGTT
(a) Plasma glucose concentration obtained 2 hours after a 75-g oral glucose ingestion
(b) 200 mg/dL or greater
(c) More sensitive and specific than FPG but more cumbersome to perform
iv. A1C (glycated hemoglobin)
(a) 6.5% or greater
(b) May be less sensitive than FPG in identifying mild diabetes, but does not require fasting and has less variability from day to day
(c) A1C values may be inaccurate in patients with anemia, chronic malaria, sickle cell anemia, pregnancy, or significant blood loss or recent blood transfusion.
v. Unless a clinical diagnosis is clear, including symptoms of hyperglycemia, diagnosis requires two abnormal tests showing hyperglycemia and can be obtained from the same sample (using two of the above criteria) or in two separate test samples (can be the same type of test).

b. Other useful diagnostic tests if type of DM is in question
i. C-peptide (measure of endogenous insulin secretion, usually negligible in T1D and normal or elevated early in T2D)
ii. Presence of islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase, or tyrosine phosphatase (all suggest autoimmune activity)

2. Gestational diabetes diagnosis: Glycemic values in pregnancy
a. Updated and simplified diagnostic criteria
b. "One-step" approach: 75-g OGTT at 24–28 weeks' gestation
i. Fasting: 92 mg/dL or greater
ii. 1 hour after OGTT: 180 mg/dL or greater
iii. 2 hours after OGTT: 153 mg/dL or greater
c. "Two-step" approach: 50-g OGTT (nonfasting) at 24–28 weeks' gestation
i. If 1 hour after 50-g OGTT is less than 140 mg/dL, no further workup
ii. If 140 mg/dL or greater, do additional fasting OGTT using 100 g (see the ADA guidelines for diagnostic glucose criteria)

3. Prediabetes diagnosis (high-risk population)
a. Impaired fasting glucose: FPG 100–125 mg/dL
b. Impaired glucose tolerance: 2-hour plasma glucose after OGTT (75 g) of 140–199 mg/dL
c. A1C 5.7%–6.4%
d. Screen yearly for T2D if positive for prediabetes

Patient Case

7. A 56-year-old man with T2D takes metformin 1000 mg twice daily. He has no other chronic diseases or history of cardiovascular disease. His current vital signs and laboratory results are as follows: blood pressure 148/78 mm Hg, heart rate 74 beats/minute, and A1C 6.9%. Which agent, if added to the current regimen, has the most potential to reduce both microvascular and macrovascular complications in this patient?

A. Insulin glargine.

B. Lisinopril.

C. Glyburide.

D. Niacin.

E. Goals of Diabetes Management in Nonpregnant Adults
   1. Primary goal: Prevent the onset of acute or chronic complications
   2. Acute complications: Hypoglycemia, diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic syndrome
   3. Chronic complications
      a. Microvascular: Retinopathy, nephropathy, and neuropathy
      b. Macrovascular: Cardiovascular, cerebrovascular, and peripheral vascular diseases
   4. Glycemic therapy goals
      a. A1C less than 7.0% (Note: The American College of Endocrinology/AACE guidelines recommend 6.5% or less.)
         i. Obtain every 6 months in patients at goal A1C and every 3 months in those over goal.
         ii. Less-stringent A1C targets may be appropriate in those with a short life expectancy (e.g., terminal cancer), advanced diabetic complications, longstanding diabetes that is difficult to control (e.g., frail older adults with a history of hypoglycemia at risk of falls), or extensive other comorbidities (clinical atherosclerotic cardiovascular disease). (In such situations, a higher A1C [e.g., less than 8%] may be sufficient to limit the risk of acute complications of hyperglycemia such as dehydration and electrolyte deficiencies while preventing exacerbation of comorbidities.)
      b. FPG or premeal 80–130 mg/dL. Frequency of monitoring depends on regimen, type of DM, and current glycemic control.
      c. Peak postprandial glucose (1–2 hours after a meal) less than 180 mg/dL
      d. Time in glycemic range 70% or greater and time below range less than 4% (for patients with continuous glucose monitoring systems)
   5. Non-glycemic therapy goals
      a. Blood pressure
         i. The ADA recommends a blood pressure goal of less than 130/80 mm Hg in patients at high risk of cardiovascular disease (existing cardiovascular disease or greater than a 15% ten-year risk) and a goal of less than 140/90 mm Hg in those at lower risk.
         ii. ACC/AHA hypertension guidelines recommend less than 130/80 mm Hg.
      b. Lipids
         i. ADA: No specific LDL goal is currently recommended.
         ii. ACC/AHA 2018 guidelines suggest lowering LDL by 30%–49% in patients with diabetes age 40–75 and by at least 50% if at higher risk, e.g. age 50-75 or patient has other risk factors.
         iii. No specific TG or HDL goals are currently recommended.

F. Goals for Gestational Diabetes
   1. Primary goal: Prevent complications to mother and child.
   2. Glycemic therapy goals (more stringent)
      a. FPG of 95 mg/dL or less
      b. 1-hour postprandial glucose 140 mg/dL or less
      c. 2-hour postprandial glucose 120 mg/dL or less
   3. Potential complications of hyperglycemia during pregnancy
      a. Mother: Hypertension, preeclampsia, T2D after pregnancy
      b. Fetus/child: Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome

G. Benefits of Optimizing Diabetes Management in Nonpregnant Adults
   1. Glycemic control
      a. Reduces the risk of developing retinopathy, nephropathy, and neuropathy in T1D and T2D
      b. Prospective studies, specifically designed to assess optimizing glycemic control and effect on cardiovascular events, have shown little or no reduction in cardiovascular outcomes.
      c. However, the "legacy" effect (also known as "metabolic memory") in the Diabetes Control and Complications Trial of T1D and the UK Prospective Diabetes Study of T2D suggests early control has future cardiovascular benefit.
      d. No profound benefit of aggressive glycemic control in T2D (A1C less than 6.5%)
   2. Blood pressure control: Reduction in both macrovascular and microvascular complications
   3. Lipid control: Reduction in LDL with moderate-intensity statin therapy reduces cardiovascular complications.

Patient Case

8. A 21-year-old patient (weight 80 kg) is given a diagnosis of T1D after the discovery of elevated glucose concentrations (average 326 mg/dL), and the patient has signs and symptoms of hyperglycemia. Which is the most appropriate initial dose of rapid-acting insulin before breakfast for this patient? (Assume a TDI regimen of 0.5 unit/kg/day.)

   A. 2 units.

   B. 4 units.

   C. 7 units.

   D. 14 units.

H. Therapeutic Management of T1D (Table 3)
   1. Insulin agents
      a. Categorized on the basis of duration after injection
         i. Rapid acting: Insulin aspart (two formulations), lispro, (two formulations) glulisine, and inhaled insulin
         ii. Short acting: Regular human insulin
         iii. Intermediate acting: Neutral protamine Hagedorn (NPH)
         iv. Long acting: Insulin glargine, degludec and detemir
      b. Combination insulin products (intermediate or long acting, regular or rapid acting): 70/30, 75/25, insulin degludec and glargine available in combination with GLP-1 agonist
      c. Higher-concentration insulin products
         i. More commonly used in patients with T2D needing significant daily insulin doses
         ii. U-300 glargine (300 units/mL), U-200 degludec (200 units/mL), U-200 lispro (200 units/mL), U-500 regular insulin (500 units/mL)

Table 3. Characteristics of U-100 (100 units/mL) Insulins[a]

Category	Drug Name	Clarity	Onset	Administration Time Before Meal (min)	Peak (hr)	Duration (hr)
Rapid acting	Aspart Lispro Glulisine Inhaled insulin	Clear	15–30 min	15 (shorter with fast-acting aspart/lispro) (inhaled insulin at beginning of meal)	1–3 (shorter with inhaled and fast-acting aspart/lispro)	2–5 (shorter with inhaled and fast-acting aspart/lispro)
Short acting	Regular	Clear	30–60 min	30	2–3	4–6
Intermediate acting	Neutral protamine Hagedorn	Cloudy	1–2 hr	N/A	4–8	10–20
Long acting	Detemir Glargine Degludec	Clear	2–4 hr 1–2 hr 1–2 hr	N/A	6–8 "Peakless" "Peakless"	6–24 ~24 24–42

[a]The times given depend on the source of data and intersubject variability.

N/A = not applicable.

d. Glycemic target
    i. Regular- and short-acting insulins target postprandial glucose concentrations.
    ii. Intermediate- and long-acting insulins target fasting glucose concentrations.
e. Inhaled insulin may cause bronchospasm and is contraindicated in patients with asthma, chronic obstructive pulmonary disease, or lung cancer. Requires spirometry testing at baseline, at 6 months of therapy, and annually thereafter

2. Management of insulin therapy
    a. First step is to estimate TDI requirements.
    b. Weight-based estimate if insulin naive
        i. 0.3–0.6 unit/kg/day
        ii. Requirements higher if treating DKA near initial diagnosis of DM
        iii. Honeymoon phase shortly after treatment initiation often requires lower daily insulin needs.
    c. With older insulin formulations (NPH and regular insulin)
        i. Two-thirds of TDI is given before the morning meal. Two-thirds of this is given as NPH, and one-third is given as regular insulin.
        ii. One-third of TDI is given before the evening meal. Either with two-thirds given as NPH and one-third given as regular insulin or in a 1:1 ratio. Alternative is regular given before evening meal and NPH at bedtime.
        iii. Advantages: Daily insulin injection frequency two or three times daily and less expensive than newer insulins
        iv. Disadvantages: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events
    d. Basal-bolus insulin therapy (i.e., physiologic insulin therapy)
        i. Use insulin analogs to better mimic natural insulin secretion patterns
        ii. Use long-acting basal insulin to prevent ketosis and control FPG
        iii. Use bolus insulin to control postprandial hyperglycemia
        iv. Basal insulins: Insulin glargine or degludec once daily or insulin detemir once or twice daily
        v. Bolus insulins: Rapid-acting insulin (can use short-acting insulin)
        vi. Basal requirements are typically 50% of estimated TDI, but some practitioners may prefer more or less.

vii. Bolus requirements are typically 50% of estimated TDI split three ways before meals.
(a) Provides initial estimate of prandial insulin needs
(b) Typically, patients begin to estimate bolus requirements given the amount of carbohydrates to be ingested. Requires significant patient education in food carbohydrate estimates
(c) Alternative bolus requirement (Rule of 500): Dividing 500 by TDI will estimate the amount of carbohydrates (in grams) that 1 unit of a rapid-acting insulin will cover.
viii. Advantages over NPH plus regular approach: More physiologic, less hypoglycemia, more flexible to patient mealtimes
ix. Disadvantages: Cost and increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately). Note that the same process of basal-bolus insulin therapy can apply to a patient with T2D who is receiving intensive insulin therapy with or without oral DM medications.

e. Correctional insulin needs
i. Always a need to correct for hyperglycemic excursions, despite optimal basal-bolus therapy
ii. "1800 rule": 1800/TDI = milligrams per deciliter of glucose lowering per 1 unit of rapid-acting insulin
(a) For example, if TDI is 60 units, 1800/60 = 30, suggesting that 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
(b) Also called *insulin sensitivity factor*
(c) Alternative: "1500 rule" when using regular human insulin (i.e., 1500/TDI)
iii. More patient-specific than traditional sliding-scale insulin

f. Continuous glucose monitoring (CGM)
i. Used with or without insulin pumps
ii. Real-time CGM (continuously transmits glucose data to sensor or smart device)
iii. Intermittent CGM (requires scanning by a sensor to view glucose data)

g. Continuous subcutaneous insulin infusion (insulin pump)
i. Device allows patient-specific hourly basal dosing and bolus insulin dosing.
ii. Uses rapid-acting insulins
iii. Requires patient education and carbohydrate counting
iv. Used in conjunction with continuous glucose monitoring devices. Technology is rapidly advancing (newest systems, called "hybrid closed-loop systems," act almost as an artificial pancreas).

h. Assessing therapy and dosage adjustment
i. Know the goals for fasting and postprandial glucose concentrations.
ii. Identify when patient is at goal and not at goal (hypoglycemia or hyperglycemia). Look for consistent trends rather than isolated events.
iii. Identify which insulin affects problematic glucose concentrations.
iv. Adjust insulin dosage or patient behavior accordingly.
v. Same process for treating T2D applies (see text that follows)

3. Amylin analog
a. Mechanism of action: Amylin is cosecreted with insulin and has effects similar to those of GLP-1 described in the text that follows.
b. Pramlintide is currently the only agent in this class available in the United States. Pramlintide can be used in either T1D or T2D as adjunctive therapy in patients receiving insulin.
c. Dosing
i. T1D
(a) Initial: 15 mcg subcutaneously immediately before main meals
(b) Must reduce dosage of preprandial rapid-acting, short-acting, or combination insulin products by 50%

(c) Maximal daily dosage is 60 mcg with each meal.
(d) Dosage should be titrated in 15-mcg increments, as tolerated, but no more rapidly than every 3 days.

ii. T2D
(a) Initial: 60 mcg subcutaneously immediately before main meals
(b) Must reduce preprandial insulins by 50%
(c) Maximal daily dosage: 120 mcg with each meal
(d) Dosage should be titrated in 60-mcg increments, as tolerated, but no more rapidly than every 3–7 days.

iii. Use of prefilled pens is strongly recommended, when possible, rather than a syringe and vial, to reduce the risk of dosing errors (dosing instructions with U-100 syringes and vial in package insert).

iv. Cannot be mixed with insulin products; requires increased frequency of daily injections

d. Adverse effects
i. Boxed warning for severe hypoglycemia, especially in patients with T1D
ii. Nausea, vomiting, anorexia, headache

e. Contraindications and precautions
i. Substantial gastroparesis
ii. History of poor adherence or monitoring of BG
iii. A1C greater than 9%
iv. Hypoglycemia unawareness or frequent bouts of hypoglycemia

f. Efficacy
i. A 0.5%–1% reduction in A1C
ii. Effective at controlling postprandial glucose excursions

Patient Cases

9. A 55-year-old man with T2D for 6 months has been receiving metformin 1000 mg twice daily since his diagnosis. His A1C today is 8.2%. His morning fasting blood glucose (FBG) readings are consistently at goal. His after-meal glucose readings average 210–230 mg/dL. The patient states that he is worried about his weight and does not want to add a medication that might increase it. Which would be most appropriate for this patient?

A. Glyburide.
B. Liraglutide.
C. Pioglitazone.
D. Insulin glargine.

10. A 66-year-old man has had T2D for 4 years. His A1C today is 7.7%. He has altered his diet and states that he has been exercising regularly for months. He takes metformin 1000 mg twice daily. Which would best help optimize his glycemic control?

A. Continue current medications and counsel to improve his diet and exercise.
B. Discontinue metformin and initiate exenatide 5 mcg twice daily.
C. Add bromocriptine 0.8 mg at bedtime.
D. Add sitagliptin 100 mg once daily to his metformin therapy.

I. Therapeutic Management of T2D
1. Given the progressive nature of T2D, a stepwise approach is usually needed.
2. ADA treatment recommendations for hyperglycemia emphasize a patient-centered approach to care, considering patient preferences, needs, and values.

3. Metformin remains the initial drug of choice, unless contraindicated or adverse effects preclude its use or if improvements in exercise and diet early after diagnosis fail to control hyperglycemia. (Consider combination therapy of metformin with the medications listed in the text that follows if baseline A1C is 1.5% or greater above personal goal A1C.)
4. If metformin monotherapy fails to allow the patient to attain or maintain glycemic control, adding other agents is based on several criteria and weighs the advantages and disadvantages of the various oral and injectable agents.
    a. Efficacy in lowering A1C (also focus on ability to lower fasting or postprandial glucose concentrations or both)
    b. Existing comorbidities. The following agents that may be added to or replace metformin for patients with established cardiovascular disease, heart failure, or renal insufficiency:
        i. Cardiovascular disease: Consider GLP-1 agonist or SGLT-2 inhibitor
        ii. Heart failure or chronic kidney disease: Consider SGLT-2 inhibitor
    c. Risk of hypoglycemia
    d. Effects on weight
    e. Adverse effect profile
    f. Cost
    g. Oral or injection patient preference
5. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, GLP-1, GIP/GLP-1 agonists, and basal insulin are preferred to less efficacious options or agents with a higher adverse risk profile.
6. Adding injectable medications to existing oral DM agents
    a. ADA recommends GLP-1 agonists as preferred to insulin unless extreme or symptomatic hyperglycemia is present.
        i. Because of a mildly improved A1C reduction with GLP-1 agonists compared with insulin therapies
        ii. GLP-1 agonists have a lower risk of hypoglycemia and are associated with weight loss.
    b. Consider addition of a basal insulin / GLP-1 agonist combination or basal/bolus insulin regimen when significant hyperglycemia exists. ADA suggests adding either early in therapy if:
        i. A1C greater than 10% or
        ii. A1C is greater than 2% above goal
    c. Weight-based dosing: For example, 0.1–0.2 unit/kg/day of basal insulin (higher dosages if significant hyperglycemia exists)
    d. Can increase basal insulin according to fasting glucose concentrations
    e. Can add GLP-1 agonist or SGLT-2 inhibitor if weight gain is a concern or bolus insulin to one or more meals if postprandial glucose is a concern after initiating basal insulin
    f. Insulin secretagogues should be lowered in dosage or discontinued altogether when bolus insulin added to reduce risk of hypoglycemia
    g. Thiazolidinediones should be lowered or discontinued when basal or bolus insulin is added to the regimen because of the increased risk of edema.
7. Changing from oral DM medications to insulin-only management (e.g., because of adverse effects, contraindications, lack of efficacy of oral medications)
    a. Can follow NPH/regular insulin or basal-bolus approach similar to that in T1D described earlier
    b. The TDI requirements in T2D are usually much higher than in T1D because of insulin resistance.

J. Therapeutic Agents in T2D
    1. Metformin (biguanide)
        a. Mechanism of action: Reduces hepatic gluconeogenesis; also favorably affects insulin sensitivity and, to a lesser extent, intestinal absorption of glucose

b. Dosing
   i. Initial: 500 mg once or twice daily (once daily with extended-release formulation)
   ii. Maximal daily dose: 2550 mg (more commonly, 2000 mg/day)
   iii. Can increase at weekly intervals as necessary
   iv. Small initial dosage and slow titration secondary to GI disturbances
c. Adverse effects
   i. Common: Nausea, vomiting, diarrhea, epigastric pain
   ii. Less common: Decrease in vitamin B_{12} concentrations (monitor periodically), lactic acidosis (rare)
   iii. Signs or symptoms of lactic acidosis include acidosis, nausea, vomiting, increased respiratory rate, abdominal pain, shock, and tachycardia.
d. Contraindications and precautions (because of risk of lactic acidosis)
   i. Renal impairment (contraindicated because of increased risk of lactic acidosis)
      (a) Discontinue if eGFR is less than 30 mL/minute/1.73 m^2, and initiating if eGFR is 30–45 mL/minute/1.73 m^2 is not recommended. Assess benefit of continuing use in patients already prescribed metformin if eGFR is 30–45 mL/minute/1.73 m^2 and consider a 50% dose reduction.
      (b) Monitor renal function every 3–6 months in patients with eGFR of 45–60 mL/minute/1.73 m^2 and every 3 months if 30–45 mL/minute/1.73 m^2
   ii. Age 80 or older (use caution and carefully assess renal function)
   iii. High risk of cardiovascular event or hypoxic state
   iv. Hepatic impairment
   v. Interrupt therapy in patients with eGFR of 30–60 mL/minute/1.73 m^2 if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal SCr concentrations are achieved.
e. Efficacy
   i. 1%–2% A1C reduction
   ii. Some benefit in TG reduction and weight loss
   iii. Considered first-line therapy unless contraindicated on the basis of adverse effect profile, reduction in A1C, cost, and limited data that it reduces cardiovascular events in overweight patients

2. Sulfonylureas
   a. Mechanism of action: Bind to receptors on pancreatic β-cells, leading to membrane depolarization, with subsequent stimulation of insulin secretion (insulin secretagogue)
   b. First-generation agents seldom used today (e.g., chlorpropamide, tolbutamide)
   c. Second-generation agents (e.g., glyburide, glipizide, glimepiride). Dosage titration: Can increase at weekly intervals, as necessary
   d. Adverse effects
      i. Common: Hypoglycemia, weight gain
      ii. Less common: Rash, headache, nausea, vomiting, photosensitivity
      iii. Rare: Lactic acidosis
   e. Contraindications and precautions
      i. Hypersensitivity to sulfonamides
      ii. Patients with hypoglycemic unawareness
      iii. Poor renal function (glipizide may be a better option than glyburide or glimepiride in older adults or in those with renal impairment because drug or active metabolites are not renally eliminated)
   f. Efficacy
      i. 1%–2% A1C reduction
      ii. Note: For this and all medications used to treat hyperglycemia, the absolute decrease in A1C is larger for higher baseline A1C values and smaller for lower A1C values.

Table 4. Second-Generation Sulfonylurea Dosing Strategies

Drug	Initial Dosage	Maximum Daily Dosage (mg)
Glyburide (not micronized)	2.5–5.0 mg once or twice daily	20
Glyburide (micronized)	1.5–3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40 (little improved efficacy > 20 mg/day)
Glimepiride	1–2 mg once daily	8

3. Meglitinides
    a. Mechanism of action: Similar to that of sulfonylureas in increasing insulin secretion from the pancreas, but with a more rapid onset and shorter duration of activity
    b. Glucose-dependent activity
    c. Two currently available: Repaglinide and nateglinide
    d. Dosing
        i. Repaglinide
            (a) Initial: 0.5–1 mg 15 minutes before meals
            (b) Maximal daily dosage: 16 mg
        ii. Nateglinide
            (a) 120 mg before meals
            (b) 60 mg if A1C near goal
        iii. Repaglinide can be increased in weekly intervals, if needed.
    e. Adverse effects: Hypoglycemia (though less than with sulfonylureas), weight gain, upper respiratory infection
    f. Contraindications and precautions
        i. Hypersensitivity
        ii. Caution in concomitant use of repaglinide and gemfibrozil: Can lead to greatly increased repaglinide concentrations
    g. Efficacy
        i. 0.5%–1.5% A1C reduction (repaglinide reduces A1C more than nateglinide)
        ii. Most effective on postprandial glucose excursions
4. Thiazolidinedione (often called *glitazones* or *TZDs*)
    a. Mechanism of action
        i. Peroxisome proliferator–activated receptor γ-agonist
        ii. Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity
    b. Dosing
        i. Pioglitazone
            (a) Initial: 15 mg once daily
            (b) Maximal daily dosage: 45 mg
        ii. Dosage titration is slow, and the maximal effect of a dosage change may not be observed for 8–12 weeks.
    c. Adverse effects
        i. Weight gain
        ii. Fluid retention (particularly peripheral edema) is worse with insulin use and is dose-dependent. Edema is less responsive to diuretic therapy. Macular edema can result.
        iii. Risk of proximal bone fractures; use caution in patients with existing osteopenia or osteoporosis (discontinuation reduces risk)

iv. Possible risk of bladder cancer with pioglitazone (dosage and duration of use dependent). Data are contradictory.
v. Increased risk of heart failure
(a) Boxed warning
(b) More than a 2-fold higher relative risk, although absolute risk is quite small

d. Contraindications and precautions
i. Hepatic impairment
ii. Class III/IV heart failure (symptomatic heart failure)
iii. Existing fluid retention

e. Efficacy
i. 0.5%–1.4% A1C reduction
ii. May help improve HDL as well

5. DPP-4 inhibitors
a. Mechanism of action: Inhibit the breakdown of GLP-1 secreted during meals, which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety
b. Dosing
i. Sitagliptin: 100 mg once daily
(a) Reduce dosage with CrCl if 30–49 mL/minute/or greater to 50 mg once daily.
(b) Reduce dosage with CrCl less than 30 mL/minute to 25 mg once daily.
ii. Saxagliptin: 5 mg once daily
(a) Reduce dosage with CrCl of 50 mL/minute or less to 2.5 mg once daily.
(b) Reduce dosage when coadministered with strong CYP3A4/5 inhibitor (e.g., ketoconazole) to 2.5 mg once daily.
iii. Linagliptin: 5 mg once daily (no dosage adjustment for renal impairment)
iv. Alogliptin: 25 mg once daily
(a) Reduce dosage with CrCl of 30–59 mL/minute to 12.5 mg once daily.
(b) Reduce dosage with CrCl less than 30 mL/minute to 6.25 mg once daily.

c. Adverse effects
i. Upper respiratory and urinary tract infections, headache, severe joint pain
ii. Hypoglycemia with monotherapy is minimal, but frequency is increased with concurrent sulfonylurea therapy (can lower dosage of sulfonylurea when initiating).
iii. Sitagliptin has had some postmarketing reports of acute pancreatitis, angioedema, Stevens-Johnson syndrome, and anaphylaxis.
iv. Safety studies of saxagliptin and, to a lesser extent, alogliptin (but not sitagliptin or linagliptin) have shown an increased risk of heart failure hospitalization. In 2017, the FDA recommended warnings to package labeling of all DPP-4 inhibitors.

d. Contraindications and precautions
i. Previous hypersensitivity to the agents
ii. History of pancreatitis

e. Efficacy: 0.5%–0.8% reduction in A1C, considered weight neutral

6. SGLT-2 inhibitor
a. Mechanism of action: Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule; has some effect on delaying GI glucose absorption
b. Dosing
i. Canagliflozin
(a) 100 mg once daily before the first meal of the day
(b) Maximal daily dosage: 300 mg
(c) Reduce dosage with eGFR of 30–59 mL/minute/1.73 m^2 to 100 mg daily.
(d) Discontinue or do not initiate if eGFR is less than 30 mL/minute/1.73 m^2.

ii. Dapagliflozin
    (a) 5 mg once daily in the morning (with or without food)
    (b) Maximal daily dosage: 10 mg
    (c) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m^2.
iii. Empagliflozin
    (a) 10 mg once daily in the morning (with or without food)
    (b) Maximal daily dosage: 25 mg
    (c) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m^2.
iv. Ertugliflozin
    (a) 5 mg once daily in the morning (with or without food)
    (b) Maximal daily dosage: 15 mg
    (c) Discontinue or do not initiate if eGFR is less than 60 mL/minute/1.73 m^2.

c. Adverse effects
    i. Increased urination
    ii. Urinary tract infections
    iii. Genital mycotic infections (more common in females)
    iv. Hypotension
    v. Increased hypoglycemia risk with concomitant insulin or insulin secretagogue
    vi. Class is linked with rare cases of euglycemic DKA and Fournier gangrene.
    vii. Possible increased bone fracture risk, decreased bone mineral density, and foot or leg amputation with canagliflozin
d. Contraindications and precautions
    i. Significant renal impairment (varies by agent, as stated earlier)
    ii. Suggested to ensure euvolemia before initiating agent, given its diuretic effect especially in older adults, patients with existing renal impairment or already low blood pressure, or patients receiving diuretics
    iii. Consider factors that could predispose the patient to acute kidney injury (e.g., low blood volume, chronic kidney insufficiency, heart failure, or medications that could alter kidney function).
    iv. Agent should be discontinued before any surgery to reduce the risk of ketoacidosis (3 days before with canagliflozin, dapagliflozin, and empagliflozin and 4 days before with ertugliflozin).
e. Efficacy
    i. 0.3%–1.0% reduction in A1C
    ii. Effect on both fasting and postprandial glucose concentrations
    iii. Mild weight loss
    iv. Empagliflozin, dapagliflozin, and canagliflozin can reduce cardiovascular morbidity in patients with T2D and established cardiovascular disease and may improve renal outcomes.
    v. Canagliflozin or dapagliflozin in patients with significant urine albumin excretion and renal insufficiency reduces the risk of end-stage renal disease, doubling of SCr, or renal death.
    vi. All agents within the class have been shown to reduce heart failure admissions in patients with T2D with or without a history of heart failure.

Patient Case

11. A 66-year-old man is given a diagnosis today of T2D. Two weeks ago, his A1C was 7.5% and SCr was 1.8 mg/dL (eGFR 25 mL/minute/1.73 m^2). He has a history of hypertension, dyslipidemia, and systolic heart failure (New York Heart Association class III, ejection fraction 33%). He has 2+ pitting edema bilaterally. In addition to improvements in diet and exercise, which is best to initiate?

    A. Linagliptin.

    B. Pioglitazone.

    C. Exenatide.

    D. Metformin.

7. GLP-1 analogs
    a. Mechanism of action: Synthetic analog of human GLP-1 that binds to GLP-1 receptors, resulting in glucose-dependent insulin secretion, reduction in glucagon secretion, and reduced gastric emptying; promotes satiety
    b. Approved agents: Exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide
    c. Dosing
        i. Exenatide
            (a) Twice-daily formulation (pen)
                (1) Initial: 5 mcg subcutaneously twice daily, administered no more than 60 minutes before morning and evening meals
                (2) Maximal dosage: 10 mcg twice daily
                (3) Dosage titration from 5 mcg to 10 mcg twice daily after 1 month, if tolerated
            (b) Once-weekly formulation (single-dose tray or pen, each containing lyophilized powder and diluent)
                (1) 2 mg subcutaneously once weekly
                (2) Powder must be reconstituted by patient immediately before injection.
        ii. Liraglutide (pen)
            (a) 0.6 mg subcutaneously once daily for 1 week (regardless of mealtime)
            (b) Dosage titration from 0.6 to 1.2 mg/day, if tolerated
            (c) Maximal daily dosage: 1.8 mg/day
        iii. Lixisenatide (pen)
            (a) Initial dose: 10 mcg once daily for 14 days
            (b) Maintenance dose: 20 mcg once daily
        iv. Dulaglutide (pen and single-dose syringe)
            (a) 0.75 mg subcutaneously once weekly
            (b) Dosage titration to 4.5 mg once weekly for additional glycemic control
        v. Semaglutide (pen and single-dose syringe and oral formulation)
            (a) 0.25 mg subcutaneously once weekly
            (b) Dosage titration to 2 mg once weekly at monthly intervals for additional glycemic control
            (c) Oral formulation is dosed starting with 3 mg once daily and increased at monthly intervals to a maximum dose of 14 mg daily.
    d. Adverse effects
        i. Nausea, vomiting, diarrhea common, but can subside or cease over time
        ii. Hypoglycemia common with concurrent sulfonylurea or insulin (consider reduction in sulfonylurea or insulin dose)
        iii. Postmarketing reports of pancreatitis and acute renal failure or impairment

e. Contraindications and precautions
    i. Impaired renal function: CrCl less than 30 mL/minute for either exenatide formulation; less specific for liraglutide. No dose adjustment necessary with semaglutide
    ii. Caution with a history of severe GI tract disorder, particularly gastroparesis
    iii. History of pancreatitis
    iv. For liraglutide, semaglutide, dulaglutide, once-weekly exenatide: Contraindicated in patients with a personal or family history of medullary thyroid carcinoma (adverse effect found in rodent studies but not in humans)
f. Efficacy
    i. A 0.5%–1.5% reduction in A1C
    ii. Effects on postprandial hyperglycemia better than on fasting glucose concentrations with once- or twice-daily formulations
    iii. Improved A1C, fasting glucose reduction, and nausea or vomiting with once-weekly than with twice-daily exenatide formulation
    iv. Modest weight loss
    v. Liraglutide, dulaglutide, exenatide, and semaglutide have been shown to reduce some cardiovascular outcomes in high-risk patients, whereas lixisenatide has not, question whether class effect because populations studied in cardiovascular outcomes trials differed greatly with respect to percentages of those with existing cardiovascular disease

8. GLP-1/glucose-dependent insulinotropic polypeptide agonist
    a. Mechanism of action: Similar to GLP-1 agonists above
    b. Tirzepatide is the only agent currently approved for treatment of T2D.
    c. Dosing
        i. Initial: 2.5 mg subcutaneously once weekly
        ii. Increase at monthly intervals to 5, 10, or 15 mg once weekly
    d. Adverse effects: Similar to GLP-1 agonists
    e. Contraindications and precautions: Similar to GLP-1 agonists
    f. Efficacy
        i. 2.0%–2.3% reduction in A1c, also decreases body weight
        ii. Targets both fasting and postprandial glucose excursions
9. α-Glucosidase inhibitors
    a. Mechanism of action: Slows the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars
    b. Two agents available: Acarbose and miglitol
    c. Dosing (both agents dosed similarly)
        i. Initial: 25 mg three times daily at each meal
        ii. Maximum daily dosage: 300 mg
        iii. Slow titration, increasing as tolerated every 4–8 weeks to minimize GI adverse effects
    d. Adverse effects
        i. Flatulence, diarrhea, abdominal pain
        ii. Increased liver enzymes with high doses of acarbose
    e. Contraindications and precautions: Inflammatory bowel disease, colonic ulcerations, intestinal obstruction
    f. Efficacy
        i. 0.5%–0.8% reduction in A1C, also shown to decrease body weight
        ii. Targets postprandial glucose excursions
        iii. Might not be as effective in patients using low-carbohydrate diets

10. Bile acid sequestrant:
    a. Mechanism of action
        i. Bile acid sequestrant used primarily for cholesterol management. Its mechanism to reduce serum glucose concentrations is not clearly understood. Colesevelam is thought to be an antagonist to the farnesoid X receptor, which subsequently reduces hepatic gluconeogenesis. By reducing bile acid absorption, colesevelam reduces farnesoid X receptor activity.
        ii. Used in conjunction with insulin or oral DM medications
    b. Colesevelam is the only studied and approved drug in this class.
    c. Dosing: Six 625-mg tablets once daily or three 625-mg tablets twice daily
    d. Adverse effects: Constipation, dyspepsia, nausea, myalgia
    e. Contraindications and precautions
        i. Contraindicated in patients with a history of bowel obstruction or serum triglyceride concentrations greater than 500 mg/dL
        ii. Caution in patients with swallowing disorders (large pill), dysphasia, gastric mobility disorders, and serum triglyceride concentrations greater than 300 mg/dL
    f. Efficacy: 0.3%–0.5% reduction in A1C
11. Bromocriptine
    a. Mechanism of action: Not clearly understood. Agonist for dopamine receptor D_2 is thought to reset circadian rhythm, which can reduce caloric intake and storage. Other effects may be through α_1-antagonism, α_2-agonistic properties, and modulation of serotonin and prolactin.
    b. Dosing
        i. Initial: 0.8 mg once daily on waking; take with food (increases bioavailability)
        ii. Maximal daily dosage: 4.8 mg
        iii. Titrate weekly by 0.8 mg/day as tolerated and according to response.
        iv. Tablet strength differs from generic formulations currently on the market.
    c. Adverse effects: Nausea, somnolence, fatigue, dizziness, vomiting, headache, orthostatic hypotension, syncope
    d. Contraindications and precautions
        i. Can limit the effectiveness of agents used to treat psychosis or exacerbate psychotic disorders
        ii. Should not be used in nursing mothers or patients with syncopal migraines
        iii. Concomitant use with dopamine antagonists (e.g., neuroleptic agents) can limit the efficacy of both agents.
    e. Efficacy (Table 5)
        i. 0.1%–0.6% reduction in A1C
        ii. Possible cardiovascular benefit

Table 5. Comparison of Therapies for Type 2 Diabetes Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations and Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens β cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improved insulin sensitivity and pancreatic function Low risk of hypoglycemia Possible cardiovascular benefit Cost	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk?
α-Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus Weight loss	GI adverse effect profile Mealtime dosing Modest A1C effect
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk? Modest A1C effect Possible increased heart failure risk (saxagliptin) Cost
GLP-1 agonist and GIP/GLP-1 agonist	Once- or twice-daily formulations have prandial focus Once-weekly formulations affect both fasting and prandial	Greater effect on prandial glucose Weight loss Efficacy Improves pancreatic function? Cardiovascular benefit (liraglutide, semaglutide, dulaglutide, and exenatide)	Nausea and vomiting Injection-site effects Questionable pancreatitis or thyroid cancer risk? Cost
Colesevelam	Prandial	Lipid benefits No systemic absorption	Large pill size and burden GI adverse effect profile Small decrease in A1C Avoid with high TG
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia Possible cardiovascular benefit	Small decrease in A1C Central nervous system adverse effects
SGLT-2 inhibitors	Fasting and prandial	Low risk of hypoglycemia Efficacy Weight loss Possible heart failure, cardiovascular, and renal benefit	Urinary tract and genital infections Diuresis Euglycemic DKA?
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection-site effects GI adverse effects
Insulin	Basal: Fasting Bolus: Prandial	Significant A1C reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection-site effects

DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP = glucagon-like peptide; SGLT = sodium glucose cotransporter.

Information adapted from: Davies M, D'Alessio D, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701; Garber A, Abrahamson M, Barzilay J, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2018 executive summary. Endocr Pract 2018;24:91-120.

K. Treatment of Inpatient DM (non–critically ill population)
   1. Joint guidelines from the ADA and AACE. The Endocrine Society also has guidelines.
   2. Strong association between admission hyperglycemia and worse inpatient outcomes and length of stay. Outcomes are worse in those who have stress-related hyperglycemia or are not known to have diabetes previously.
   3. Glycemic goal: 140–180 mg/dL
   4. Treatment
      a. Assess glucose concentrations before meals and at bedtime, if eating (every 4–6 hours if taking nothing by mouth [NPO] or receiving continuous tube feedings).
      b. Threshold for initiating therapy is 180 mg/dL or greater.
      c. According to the guidelines, subcutaneous insulin administration is the most practical way to improve hyperglycemia.
      d. Oral diabetes agents are generally not recommended unless the patient is clinically stable and eating regularly, and no significant precautions or contraindications for their use exist.
      e. Use of sliding-scale insulin alone is not recommended.
      f. Basal-bolus insulin therapy as described earlier in the treatment of T1D is recommended unless the patient is NPO. If NPO, use basal insulin alone

VII. TREATMENT OF DIABETES MELLITUS COMPLICATIONS

Patient Case

12. A patient with newly diagnosed T2D is screened for diabetic nephropathy. The following laboratory values are obtained today: blood pressure 129/78 mm Hg, heart rate 78 beats/minute, urine albumin/creatinine 27 mg/g, and estimated CrCl 94 mL/minute/1.73 m^2. Which would be the most appropriate treatment strategy?
    A. No change in therapy is warranted.
    B. Add an angiotensin-converting enzyme (ACE) inhibitor.
    C. Add a thiazide-like diuretic.
    D. Reduce daily protein intake.

A. Hypoglycemia
   1. Degree of intervention depends on glucose concentrations and presence of symptoms.
   2. Symptoms are patient-specific but can include anxiousness, sweating, nausea, tachycardia, hunger, and clammy skin.
   3. Consequences of significant hypoglycemia are most worrisome in the very young, older adults, and those with established heart disease.
   4. Assess at every clinic visit, including frequency, causes, or risks of such.
   5. Classification (according to ADA recommendations)
      a. Level 1: Plasma glucose of 70 mg/dL or less with or without symptoms
      b. Level 2: Clinically significant hypoglycemia: Plasma glucose less than 54 mg/dL
      c. Level 3: A severe event characterized by altered mental and/or physical status requiring assistance
   6. Treatment
      a. Mild to moderate hypoglycemia
         i. Oral ingestion of 15–20 g of glucose or equivalent
         ii. Repeat glucose concentration in 15 minutes and, if still less than 70 mg/dL, repeat ingestion of glucose.
         iii. Once glucose is normalized, ingest snack or meal.

b. Clinically significant hypoglycemia (altered consciousness, needs assistance from others)
    i. Glucagon 1 mg subcutaneously or intramuscularly or 3 mg by nasal inhalation
    ii. Intravenous dextrose if patient does not respond to glucagon
    iii. Raise glucose targets for several weeks.

B. Diabetic Ketoacidosis
1. More common in T1D but can occur in T2D
2. Usually occurs because of a precipitating factor that stresses the body, resulting in increased counter-regulatory hormones
    a. Inappropriate (including nonadherence) or inadequate insulin therapy and infection are the two most common causes.
    b. Other causes: Myocardial infarction, pancreatitis, stroke, drugs (e.g., corticosteroids)
3. Results in significant hyperglycemia, dehydration, and ketoacidosis
4. Common signs and symptoms: Polyuria, polydipsia, vomiting, dehydration, weakness, altered mental status, coma, abdominal pain, Kussmaul respirations, tachycardia, hyponatremia, hyperkalemia
5. Treatment
    a. Treat underlying cause, if known.
    b. Fluid replacement
        i. 0.45%–0.9% sodium chloride, depending on baseline serum sodium concentrations
        ii. Change to 5% dextrose with 0.45% sodium chloride when serum glucose is less than 200 mg/dL.
    c. Insulin
        i. Goal is to stop ketosis, not to normalize glucose concentrations.
        ii. Intravenous bolus regular insulin: 0.1 unit/kg
        iii. Intravenous infusion
            (a) 0.1 unit/kg/hour regular insulin (increase if not a 50- to 75-mg/dL decrease in serum glucose in the first hour)
            (b) Alternatively, 0.14 unit/kg/hour if no insulin bolus is given
            (c) If not at least a 10% decrease in serum glucose attained in first hour, give 0.14-unit/kg intravenous bolus
            (d) Reduce infusion rate to 0.02–0.05 unit/kg/hour when serum glucose reaches 200 mg/dL, and keep glucose of 150–200 mg/dL until DKA resolves.
        iv. Interrupt insulin treatment if baseline serum potassium is less than 3.3 mEq/L and until corrected.
    d. Potassium
        i. Potassium 20–30 mEq/L of intravenous fluid if baseline serum potassium greater than 3.3 but less than 5.3 mEq/L
        ii. Hold if 5.3 mEq/L or greater initially. Monitor and replace as needed.
        iii. Potassium 20–30 mEq/hour if baseline less than 3.3 mEq/L
    e. Intravenous bicarbonate if serum pH less than 6.9 (addition of bicarbonate is somewhat controversial)
    f. DKA considered resolved and can be converted to subcutaneous insulin when serum glucose is less than 200 mg/dL and at least two of the following:
        i. Venous pH greater than 7.3
        ii. Serum bicarbonate of 15 mEq/L or greater
        iii. Calculated anion gap of 12 mEq/L or less

C. Nephropathy
1. Screen annually with random spot collection of urine albumin/creatinine ratio, starting at diagnosis in T2D and after 5 or more years in T1D.
    a. Normal: Less than 30 mg/g (or micrograms per milligram)
    b. Increased urinary albumin excretion (albuminuria) 30 mg/g or greater

c. Two of three specimens greater than 30 mg/g obtained over 3–6 months is consistent with a diagnosis of albuminuria
d. The ADA no longer uses the terms *microalbuminuria* and *macroalbuminuria*.

2. Estimate renal function yearly (CrCl or eGFR).
3. ACE inhibitors or ARBs are considered the initial treatment of choice if urine albumin/creatinine concentrations are greater than 30 mg/g.
4. Dietary protein restriction as renal function declines
5. Canagliflozin or dapagliflozin in patients with decreased renal function and significantly elevated albuminuria reduces decline in eGFR and risk of developing end-stage renal disease
6. If the patient is unable to tolerate or has contraindication to an SGLT2 inhibitor, consider adding the nonsteroidal mineralocorticoid antagonist finerenone.

D. Retinopathy
1. Screen annually with dilated and comprehensive eye examinations, starting at diagnosis in T2D and after 5 or more years in T1D.
2. Frequency can be reduced to every 2–3 years after one or more normal examinations.
3. Appropriately control glucose concentrations, cholesterol, and blood pressure.
4. Severe forms of retinopathy (e.g., proliferative retinopathy, macular edema) can be treated with intravitreous steroids or antivascular endothelial growth factor with or without photocoagulation.

E. DM Neuropathies
1. Can have nerve damage in any area of the body, but commonly affects the lower extremities
2. Screen for distal polyneuropathy
   a. Screen after 5 years in T1D and at diagnosis in T2D, then yearly thereafter
   b. Diminished sensitivity is a significant risk factor for diabetes-related foot ulcers and increases the need for frequent visual inspection by patients, if it exists.
3. Symptoms are patient-specific but can include numbness, burning, tingling sensation, or pain.
4. Treatment of neuropathies should focus on glycemic control to minimize disease progression. Therapies for symptomatic improvement do not prevent progression.
5. Neuropathic pain therapy
   a. ADA recommendations consider duloxetine, gabapentin, or pregabalin as initial therapy.
   b. Tricyclic antidepressants (amitriptyline, desipramine)
      i. Effective but limited because of anticholinergic effects; some recommend using secondary amine tricyclic antidepressants (e.g., desipramine, nortriptyline) because they may have less anticholinergic effect than tertiary amines (e.g., amitriptyline, imipramine)
      ii. Daily dose is less than doses used for depression.
   c. Anticonvulsants (gabapentin, lamotrigine, pregabalin)
      i. Comparative data on gabapentin and pregabalin against tricyclic antidepressants show similar efficacy with fewer adverse effects. Adverse effect profile is still significant (e.g., fatigue, dizziness).
      ii. Pregabalin is the only anticonvulsant approved for use in DM neuropathic pain.
   d. Selective serotonin reuptake inhibitor/selective serotonin and norepinephrine reuptake inhibitor (duloxetine, paroxetine, citalopram, venlafaxine)
      i. Duloxetine is the only approved agent in this category.
      ii. Duloxetine data compared with amitriptyline data show similar efficacy and expected higher anticholinergic adverse effects with amitriptyline.
      iii. Duloxetine may provide better pain reduction, with tolerability similar to that of pregabalin.
   e. Tramadol/acetaminophen: As effective as gabapentin; different adverse effect profile
   f. Opioids: Tapentadol extended release is the only approved agent in this class; no head-to-head efficacy studies

g. Topical capsaicin is an alternative therapy for those with focal pain. Would not use if pain is more diffuse or widespread

6. Gastroparesis therapy
   a. Autonomic neuropathy causes nausea and vomiting after meals because of delayed gastric emptying.
   b. Nonpharmacologic strategies
      i. More frequent but smaller meals
      ii. Homogenize food
      iii. Decrease fat and fiber in diet
      iv. Gastric pacemaker
   c. Pharmacologic treatment
      i. Metoclopramide: 10 mg orally or 15 mg intranasally before meals; risk of tardive dyskinesia or extrapyramidal reactions, chronic use should assess the benefit-risk of continued therapy
      ii. Erythromycin: 40–250 mg before meals for up to 1 month

F. Cardiovascular Disease
   1. Most common cause of morbidity and mortality and health care expenditures in DM complications
   2. Proper DM management should always focus on cardiovascular disease risk reduction (review cardiovascular chapters).
   3. Stress and continually assess the blood pressure and lipid goals described earlier.
   4. Blood pressure management
      a. Often requires more antihypertensive medications
      b. Hypertensive regimen should include an ACE inhibitor, ARB, dihydropyridine calcium channel blocker, or thiazide-like diuretic.
      c. If both hypertension and increased urine albumin excretion are present, first-line therapy is an ACE inhibitor or an ARB.
      d. Administration of at least one antihypertensive in the evening may improve blood pressure and reduce cardiovascular outcomes.
   5. Lipid management (according to the ADA)
      a. Assess fasting lipid profile annually or as needed to monitor adherence.
      b. Statin therapy recommendations are based on age and cardiovascular risk.
         i. Moderate-dose statin therapy is recommended for all patients age 40–75 without established cardiovascular disease.
         ii. High-dose statin therapy should be considered for those with multiple cardiovascular risk factors.
         iii. High-dose statin therapy is recommended for all patients with established cardiovascular disease (e.g., previous cardiovascular event or acute coronary syndrome) or several existing cardiovascular risk factors.
         iv. For patients with atherosclerotic cardiovascular disease and LDL greater than 70 mg/dL despite statin therapy, consider additional LDL-lowering therapy.
         v. Statin doses are consistent with the ACC/AHA lipid guidelines.
   6. Antiplatelet therapy
      a. Low-dose aspirin (75–162 mg/day)
         i. With existing cardiovascular disease
         ii. Consider as part of primary prevention if at an increased cardiovascular risk
      b. Clopidogrel for those intolerant of aspirin therapy
   7. Consider adding a GLP-1 agonist or SGLT-2 inhibitor with proven cardiovascular benefit (especially in patients with known heart disease).
      a. Not all agents in each class have shown benefit in reducing cardiovascular outcomes.
      b. SGLT-2 inhibitors have shown a reduction in heart failure admissions in patients with or significantly at risk of cardiovascular disease.

c. GLP-1 agonists have not shown a reduction in heart failure admissions.

G. Preventive Immunizations
   1. Annual influenza vaccine
   2. Pneumococcal pneumonia vaccination (PPSV23)
   3. Hepatitis B vaccine

VIII. DIABETES INSIPIDUS

A. Diabetes insipidus (DI) is usually a result of decreased production of antidiuretic hormone, also known as *vasopressin*, in central DI, or a lack of antidiuretic hormone effect in the kidneys (nephrogenic DI).

B. Classification
   1. Central or neurogenic
      a. Idiopathic
      b. Trauma (brain injury)
      c. Neoplasm
      d. Hypodipsia
      e. Genetic abnormality
   2. Nephrogenic
      a. Genetic abnormality
      b. Acquired (more common)
         i. Drug induced (e.g., lithium, amphotericin B, foscarnet, cidofovir)
         ii. Kidney disease (e.g., polycystic kidney disease, obstruction)
         iii. Electrolyte disorder (hypercalcemia, hypokalemia)

C. Diagnosis
   1. Elevated urine volume (greater than 3 L/day)
   2. Decreased urine osmolarity (less than 200 mOsm/kg)
   3. Response to water deprivation (may help differentiate between nephrogenic and central etiology in non–critically ill patients)

D. Signs and Symptoms
   1. Polydipsia
   2. Polyuria or nocturia
   3. Weakness or lethargy
   4. Confusion or delirium (if severe)

E. Treatment
   1. Treat underlying cause, if known.
   2. Central DI
      a. Desmopressin: 5–20 mcg intranasally once or twice daily
      b. Adjunctive therapies: Chlorpropamide, carbamazepine
   3. Nephrogenic DI
      a. Thiazide diuretic
      b. Dietary sodium restriction
      c. Indomethacin

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D
Given this patient's reluctance to undergo ablative therapy, oral therapy is warranted. Methimazole (Answer D) is recommended over propylthiouracil (Answer B) because it is associated with a lower risk of hepatotoxicity, though it may not be more efficacious. Answer A is incorrect because iodine therapy is indicated in this type of case only before surgery or during an acute case of thyroid storm. Answer C is incorrect; although β-blockers might provide some symptomatic relief, they would do little to stabilize this patient's thyroid concentrations.

2. Answer: A
This patient has hypothyroidism, given her elevated TSH and low free T_4, caused by Hashimoto disease. Levothyroxine (Answer A) is the drug of choice for this condition, given its adverse effect profile, cost, antigenicity profile, and uniform potency. Although liothyronine can be used for hypothyroidism, its potential for increasing the risk of cardiovascular complications makes it second line (Answer B). Answer C is also incorrect, given its increased antigenicity compared with levothyroxine. Answer D is incorrect because it is used to treat hyperthyroidism.

3. Answer: D
Fluoxetine (Answer D), a selective serotonin reuptake inhibitor, can cause drug-induced hyperprolactinemia. Answer A is incorrect because calcium channel blockers are not associated with an elevated risk of this condition. Given the patient's normal pituitary and thyroid tests, Answer B, prolactin-secreting adenoma, is probably incorrect. Answer C is incorrect because pregnancy is not associated with an elevated risk of this condition.

4. Answer: D
Because the patient's aldosterone/renin ratio and blood pressure are high, hyperaldosteronism (Answer D) is the most likely disease listed. Cushing syndrome and hyperaldosteronism can be secondary causes of hypertension. In this case, the patient's free 24-hour urine cortisol is normal but would be elevated if he had Cushing syndrome, making Answer A incorrect. Answer B is incorrect because Addison disease is a result of cortisol deficiency and is not associated with hypertension. Answer C, hyperprolactinemia, is unlikely, given the patient's presentation and his abnormal aldosterone/renin ratio.

5. Answer: B
The minimal weight loss after 12 weeks of therapy with phentermine/topiramate should be 5%; otherwise, the medication should be discontinued. Given this patient's baseline weight, at least 5.9 kg (13 lb), Answer B, is necessary to continue therapy. The other answers provided are too low (Answer A) or exceed the 5% minimal expectation (Answers C and D).

6. Answer: D
Historically, the ADA has recommended a subsequent test of hyperglycemia to be performed at another date. Updated recommendations state that two different tests of hyperglycemia can be obtained on the same day and sample. In this case, Answer D is correct; an A1C in addition to the obtained glucose concentration can be obtained. Answers A and B would only be correct if the patient had signs or symptoms of hyperglycemia. Answer C is not recommended because the concentration has already been obtained.

7. Answer: B
Improved blood pressure control has been associated with a decrease in both microvascular (e.g., nephropathy) and macrovascular (e.g., myocardial infarction) complications. Answer B is the only option that directly affects blood pressure. Answers A and C address only hyperglycemia, which may improve microvascular complications but not macrovascular complications. Answer D, niacin, has not been shown to reduce either complication in patients with diabetes.

8. Answer: C
This patient's TDI requirement is 40 units (80 kg × 0.5 unit/kg/day). Half of this is initially used for basal insulin requirements and half for bolus insulin requirements before meals. The 20 units for bolus requirements should initially be divided equally between three meals (i.e., 6–7 units), making Answer C correct. The other three answers would provide either too much (Answer D is incorrect) or too little (Answers A and B are incorrect) estimated insulin at each meal.

9. Answer: B

The GLP-1 agonists mildly reduce weight when used to treat hyperglycemia in patients with T2D. Answer B, liraglutide, is the only GLP-1 provided. Each of the other options, a sulfonylurea (Answer A), a thiazolidinedione (Answer C), and insulin (Answer D), is associated with weight gain.

10. Answer: D

The usual next step in therapy for a patient no longer able to maintain adequate glycemic control with monotherapy is to add agents. Answer D adds to the existing metformin therapy and provides for a sufficient A1C reduction. Answer A is incorrect because the patient is already exercising and still has uncontrolled hyperglycemia. Answer B is incorrect because one agent, particularly metformin, would not normally be changed to another unless a patient were having adverse effects from the original agent. Answer C, bromocriptine, would probably not provide sufficient glycemic control, given this patient's current A1C.

11. Answer: A

In this case, initiation of medications for a patient with newly diagnosed hyperglycemia is complicated by the patient's many comorbidities. Normally, metformin, Answer D, would be the initial treatment of choice, but the patient's renal function is poor, and metformin should not be used. Answer C, exenatide, is also incorrect because it, too, should not be used in patients with significant renal impairment. Given the patient's existing edema and history of heart failure, pioglitazone (Answer B) is contraindicated because it can aggravate the conditions. Answer A, linagliptin, is the most appropriate choice because the patient's A1C is not markedly elevated, and renal function does not need to be considered.

12. Answer: A

Current recommendations call for an ACE inhibitor or an ARB if a patient has elevated urinary albumin excretion. This patient's blood pressure is at goal (less than 140/90 mm Hg), and urine albumin/creatinine is normal (less than 30 mg/g), making Answer A correct. No additional therapy is necessary. Answers B and C are incorrect because the patient's blood pressure is well controlled and urine albumin/creatinine is normal. Answer D is incorrect because protein restriction is used only after a significant decrease in CrCl, and this patient has normal renal function.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D
According to the ADA guidelines, patients with this degree of hyperglycemia should be initiated on insulin therapy, and Answer D provides an appropriate basal and bolus insulin combination. This patient's A1C is greater than 10%, and his fasting glucose is greater than 300–350 mg/dL. Answers A and C are not optimal because dual therapy with oral agents would probably not bring this patient to his glycemic goal. Answer B is also not optimal because the combination of a sulfonylurea and rapid-acting insulin would increase the risk of hypoglycemia and would probably not sufficiently reduce the A1C.

2. Answer: A
The weight-based initial estimate of total basal insulin needs is 50% of the calculated TDI. The TDI for this patient is 26 units (0.4 unit/kg/day × 65 kg). Half of that is 13 units. Answer C is incorrect; although insulin glargine is a basal insulin, the calculated dose would provide too much insulin and would likely cause significant hypoglycemia. Answers B and D are incorrect because they both use a type of insulin reserved for bolus and correctional insulin dosing. Answer A is correct because the estimated dose and type of insulin are appropriate.

3. Answer: C
This patient has an elevated blood pressure, poor renal function, and two urine albumin/creatinine concentrations above 30 mg/g. According to the ADA and the clinical literature, the best classes of medications for patients with this condition are ARBs and ACE inhibitors, making Answer C correct. Answer A (thiazide diuretic) is inappropriate because this class of medications is not as beneficial as agents that block the renin-angiotensin system. Answer B, a dihydropyridine calcium channel blocker, is incorrect for the same reason. Answer D, a non-dihydropyridine calcium channel blocker, is an alternative to agents that block the renin-angiotensin system but should not be used instead of these agents unless a patient has a contraindication.

4. Answer: B
Unlike methimazole, propylthiouracil (Answer B) has a boxed warning about the risk of hepatotoxicity. Answer A is incorrect because neither agent is considered more efficacious than the other. Answer C is incorrect because Hashimoto disease is a result of hypothyroidism, not hyperthyroidism. Methimazole is dosed once daily, whereas propylthiouracil is usually dosed up to three times daily, making Answer D incorrect.

5. Answer: A
Ketoconazole (Answer A) is used in patients with Cushing syndrome because it reduces cortisol synthesis. Answer B, spironolactone, is used in patients with hyperaldosteronism. Answer C is inappropriate because Cushing syndrome results in cortisol concentrations that are too high, and adding a corticosteroid to treat its symptoms could make the problem worse. Bromocriptine, Answer D, is used to treat acromegaly, not Cushing syndrome.

6. Answer: C
This patient has both significant renal impairment and a markedly elevated A1C. Answers A and D are incorrect because they are both contraindicated in patients with significant renal impairment. Answer B is also incorrect. Although alogliptin can be used in patients with renal impairment at a reduced dosage, it would probably not sufficiently reduce the A1C. Initiating insulin is the best option in this case because insulin can be used in patients with renal impairment and can be titrated to attain significant reductions in A1C (Answer C is correct).

7. Answer: A
An older woman with heart disease should be initiated on a lower initial dose (Answer A) of levothyroxine. Answer B is the normal starting dose (i.e., 1.6 mcg/kg) but is probably too high an initial dose for an older adult with established heart disease. Answers C and D are incorrect because the drug of choice is levothyroxine, and liothyronine is no longer recommended for this condition.

8. Answer: B
For insulin adjustments, determine which BG readings are at goal and which are not. For BG readings consistently not at goal, determine which insulin is most affecting the readings. In this case, the patient's BG readings are consistently elevated at bedtime, which is probably caused by insufficient predinner prandial (i.e.,

bolus) insulin. Increasing the predinner rapid-acting insulin, Answer B, should effectively lower the bedtime concentrations. Changing the rapid-acting insulin at other times of the day would not help, making Answers A and D incorrect. Changing the patient's basal insulin (glargine) would probably not help her bedtime BG and, because her FBG readings have been well controlled, could lead to hypoglycemia (Answer C).

9. Answer: A
This patient has mild symptoms, and her ablative therapy worked initially but now no longer controls her thyroid concentrations. Methimazole (Answer A) would be the preferred oral agent, given its dosing frequency and lower risk of hepatotoxicity compared with propylthiouracil (Answer C). Lugol's solution is used only temporarily and not chronically, making Answer B incorrect. Answer D is not optimal; β-blockers, which may provide symptomatic relief, would not significantly affect her thyroid concentrations.

10. Answer: D
This patient has good control of his fasting glucose but has postprandial hyperglycemia. An agent that targets postprandial glucose (e.g., a DPP-4 inhibitor, Answer D) would be most appropriate. Answer A is incorrect because this would exceed the maximal daily dose for metformin. Answer B is incorrect; although insulin glargine is a basal insulin that affects FPG, it has little effect on postprandial glucose. Answer C is incorrect, again because it is a basal insulin and because it is more appropriate to add medications than to change to another agent unless the patient is experiencing adverse effects with the first agent.

11. Answer: D
This patient has tried dieting and exercise, but these have failed to control her weight; thus, her current routine alone is inappropriate, making Answer A incorrect. Answer B, liraglutide, is approved for the treatment of obesity at high doses. However, this patient's A1C is at goal, and she is experiencing some bouts of low blood glucose; thus, the initial dose is too high, making this answer incorrect. Answer C is a federally scheduled medication because of its abuse potential with phentermine and, given this patient's history of substance abuse, would not be the most favorable selection, though it is not specifically contraindicated in this patient. Orlistat, Answer D, is the only agent listed to which this patient does not have a specific precaution or contraindication for its use.

12. Answer: A
This patient has now had two laboratory glycemic indicators (A1C and FBG) consistent with the diagnosis of diabetes, making Answer A correct. Answer B is probably incorrect because this patient has several risk factors for developing T2D, including obesity, ethnicity, age, a history of gestational diabetes, and a strong family history of the disease. Answer C is incorrect because there is no need to obtain another A1C reading this soon after the reading just 2 weeks ago, and the A1C can be used in the diagnosis of diabetes. Obtaining another glucose reading on another day (Answer D) is also incorrect, again because there are already two abnormal glycemic indicators; therefore, another is not necessary to confirm the diagnosis.

13. Answer: C
According to the ADA, moderate-dose statin therapy (Answer C) is recommended for patients older than 40 with diabetes but without established cardiovascular disease. In this case, the patient's glycemic and blood pressure readings are at goal (less than 7.0% and less than 140/90 mm Hg, respectively). Adding insulin (Answer A) and adding a blood pressure medication (Answer B) would not be necessary. Answer D is incorrect because this patient does not need fibrate therapy; his HDL and TG are under control.

Nephrology

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Learning Objectives

1. Categorize acute kidney injury (AKI) and chronic kidney disease (CKD) on the basis of patient history, physical examination, laboratory values, and risk factors.
2. Formulate therapeutic plans to slow progression of CKD or decrease the risk of AKI.
3. Develop a care plan to manage common complications observed in patients with CKD (e.g.- anemia, hyperphosphatemia, secondary hyperparathyroidism).
4. Interpret results of clinical trials related to the treatment of patients with kidney disease or complications.

Abbreviations in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin/creatinine ratio
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	Angiotensin II receptor blocker
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease–mineral and bone disorder
COX-2	Cyclooxygenase-2
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
FENa	Fractional excretion of sodium
FeU	Fractional excretion of urea
GFR	Glomerular filtration rate
HD	Hemodialysis
HFrEF	Heart failure with reduced ejection fraction
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in Renal Disease
MRA	Mineralocorticoid Receptor Antagonist
NSAID	Nonsteroidal anti-inflammatory drug
PTH	Parathyroid hormone
RIFLE	Risk, injury, failure, loss, end-stage (stages of AKI)
RRT	Renal replacement therapy
TSAT	Transferrin saturation

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 75-year-old man (height 73 inches, weight 92.5 kg; baseline serum creatinine [SCr] 0.9 mg/dL) presents to your institution with abdominal pain and dizziness. He has a brief history of gastroenteritis and has had nothing to eat or drink for 24 hours. His blood pressure reading while sitting is 120/80 mm Hg, which decreases to 90/60 mm Hg when standing. His heart rate is 90 beats/minute. His basic metabolic panel shows sodium (Na) 135 mEq/L, chloride (Cl) 108 mEq/L, potassium (K) 4.7 mEq/L, carbon dioxide (CO_2) 26 mEq/L, blood urea nitrogen (BUN) 40 mg/dL, SCr 1.5 mg/dL, and glucose 188 mg/dL. He has no known drug allergies. Which initial treatment of this patient's acute kidney injury (AKI) is best?
   A. Administer furosemide 40 mg intravenously × 1 dose.
   B. Insert Foley catheter to check for residual urine.
   C. Administer fluid bolus (500 mL of normal saline solution).
   D. Administer insulin lispro 3 units subcutaneously.

2. A 44-year-old man is admitted with gram-negative bacteremia. He receives 4 days of parenteral aminoglycoside therapy and develops acute tubular necrosis (ATN). Antibiotic therapy is adjusted on the basis of culture and sensitivity results. Which laboratory value is most consistent with this presentation?
   A. BUN/SCr ratio greater than 20:1.
   B. Urinalysis with no casts visible.
   C. Fractional excretion of sodium (FENa) more than 2%.
   D. Urinary sodium less than 20 mEq/L.

3. Which of the following pharmacokinetic parameters describes a drug that will be most effectively removed by hemodialysis?
   A. Serum protein binding 90% and volume of distribution of 2.5 L/kg
   B. Serum protein binding 30% and volume of distribution of 2.5 L/kg

C. Serum protein binding 90% and volume of distribution of 0.3 L/kg

D. Serum protein binding 30% and volume of distribution of 0.3 L/kg

4. A 45-year-old man (weight 59 kg, height 70 inches) has a long history of cancer. His SCr is 0.5 mg/dL. Carboplatin will be initiated, for which an accurate estimate of kidney function is critical. Which group of parameters is best to use when estimating kidney function using the Cockcroft-Gault equation?

   A. Actual body weight and measured SCr.

   B. Actual body weight and SCr rounded to 1 mg/dL.

   C. Ideal body weight and measured SCr.

   D. Ideal body weight and SCr rounded to 1 mg/dL.

5. A 59-year-old patient who has had CKD category G5D for 10 years has hypertension, coronary artery disease, mild heart failure with reduced ejection fraction (HFrEF), and type 2 diabetes. Medications are as follows: epoetin 10,000 units intravenously three times/week at dialysis, renal multivitamin once daily, atorvastatin 20 mg/day, insulin, and calcium acetate 1334 mg three times daily with meals. Laboratory values are as follows: hemoglobin (Hgb) 9.2 g/dL, parathyroid hormone (PTH) 300 pg/mL, Na 140 mEq/L, K 4.9 mEq/L, SCr 7.0 mg/dL, calcium 9 mg/dL, albumin 3.5 g/dL, and phosphorus 4.8 mg/dL. His serum ferritin concentration is 80 ng/mL and transferrin saturation (TSAT) is 14%. Mean corpuscular volume, mean corpuscular hemoglobin concentration, and white blood cell count (WBC) are all normal. He is afebrile. Which is best for managing this patient's anemia?

   A. Increase epoetin.

   B. Add oral iron.

   C. Add intravenous iron.

   D. Maintain current regimen; patient is at goal.

6. A 60-year-old patient (weight 72 kg) with a history of diabetes and hypertension is in the intensive care unit after having a myocardial infarction about 1 week ago with secondary heart failure. He now has pneumonia. He has been hypotensive for the past 5 days. Before his admission 1 week ago, his SCr was 1.0 mg/dL. His urinary output has steadily been declining for the past 3 days, despite adequate hydration, with 700 mL of urinary output in the past 24 hours. His medications include intravenous dobutamine, nitroglycerin, and cefazolin. Yesterday, his BUN and SCr were 32 and 3.1 mg/dL, respectively; today, they are 41 and 3.9 mg/dL. His urinary osmolality is 290 mOsm/kg. His urinary sodium is 45 mEq/L, and there are tubular cellular casts in his urine. Which type of AKI is this patient most likely experiencing?

   A. Prerenal azotemia.

   B. ATN.

   C. Acute interstitial nephritis (AIN).

   D. Hemodynamic/functional-mediated AKI.

7. You are evaluating a study comparing epoetin and darbepoetin with respect to their efficacy on mean Hgb concentrations. Both drugs are initiated at the recommended dose, and the Hgb concentration is checked at 4 weeks. Fifty patients are in each group. The mean Hgb in the epoetin group is 12.1 g/dL and is 12.2 g/dL in the darbepoetin group. Which statistical test is best for this comparison?

   A. Paired t-test.

   B. Independent (unpaired) t-test.

   C. Analysis of variance.

   D. Chi-square test.

8. A pharmacoeconomic study compared the use of erythropoiesis-stimulating agents with various Hgb concentrations. The primary outcome of this study was cost per quality-adjusted life-year gained. Which best describes this economic evaluation?

   A. Cost-minimization.

   B. Cost-effectiveness.

   C. Cost-benefit.

   D. Cost-utility.

9. A 58-year-old woman is being evaluated for AKI. Laboratory test results include serum sodium 134 mEq/L, BUN 35 mg/dL, SCr 1.8 mg/dL, urinary sodium 24 mEq/L, and urinary creatinine 14.3 mg/dL. Which is the best estimate of this patient's FENa?

A. 0.8%.

B. 1.25%.

C. 2.3%.

D. 4.4%.

10. A 55-year-old man has a history of hypertension. His eGFR is 48 mL/minute/1.73 m^2 and urinary albumin/creatinine ratio (ACR) is 28 mg/g. Which best depicts what this patient's goal blood pressure should be less than, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines?

A. 130/80 mm Hg.

B. 140/90 mm Hg.

C. 120/80 mm Hg.

D. 130/90 mm Hg.

11. A 66-year-old man has an eGFR of 55 mL/minute/1.73 m^2. His ACR is 100 mg/g. His Hgb is currently 13.2 g/dL, with normal red blood cell indices without treatment. Which best reflects the recommended minimum frequency of Hgb monitoring in this patient?

A. Monthly.

B. Every 3 months.

C. Every 6 months.

D. Every 12 months.

12. A 68-year-old patient has diabetes, hypertension, and an eGFR of 40 mL/minute/1.73 m^2. Medications include a renal multivitamin once daily, simvastatin, lisinopril, and hydrochlorothiazide. Laboratory values are as follows: Hgb 11.2 g/dL, immunoassay for PTH 200 pg/mL, Na 138 mEq/L, K 4.9 mEq/L, calcium 8.6 mg/dL, albumin 3.5 g/dL, phosphorus 5.8 mg/dL, and 25-hydroxyvitamin D 45 ng/mL. Which is best to prevent CKD–mineral and bone disorder (MBD) in this patient?

A. Ergocalciferol.

B. Sevelamer carbonate.

C. Calcitriol.

D. Cinacalcet.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.1–1.1.3, 1.1.6, 1.1.8, 1.1.11, 1.1.14
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.1, 1.2.2, 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1–1.3.5
2. Application of Evidence to Practice and Education
    a. 2.2. Evaluate pharmacotherapy-related literature and health information. Sub-task(s): 2.2.3, 2.2.6, 2.2.12

Patient Case

Questions 1–5 pertain to the following case.

A 48-year-old African American man (weight 70 kg) with a history of type 2 diabetes, hypertension, and osteoarthritis is admitted to the intensive care unit after an acute myocardial infarction. He was initially hypotensive, requiring 3 L of intravenous fluid. His blood pressure is now 100/65 mm Hg. Medications before admission include nicotine patch, metformin 500 mg orally twice daily, lisinopril 20 mg/day, acetaminophen 650 mg every 6 hours for joint pain, and aspirin 81 mg/daily. Before admission, his kidney function was normal (SCr 1.0 mg/dL); however, during the past 24 hours, his kidney function has declined (BUN 20 mg/dL, SCr 2.1 mg/dL). Serum sodium is 140 mEq/L and serum potassium is 4.4 mEq/L. Urinary volume has been 300 mL over the past 12 hours through urinary catheter. His urine shows muddy casts. His urinary sodium is 45 mEq/L and urinary creatinine is 20 mg/dL. He has edema and pulmonary congestion.

1. Which is the best assessment of this patient's AKI?
   A. KDIGO stage 1 AKI.
   B. KDIGO stage 2 AKI.
   C. KDIGO stage 3 AKI.
   D. Too early to assess for AKI.

2. Which best depicts this patient's FENa?
   A. 0.32%.
   B. 0.67%
   C. 1.5%.
   D. 3.4%.

3. Which is the best classification of this patient's AKI?
   A. Prerenal azotemia.
   B. Intrinsic renal disease.
   C. Postrenal obstruction.
   D. Functional AKI.

4. Which medication should be discontinued because of its risk for worsening kidney function in this patient?
   A. Lisinopril.
   B. Metformin.
   C. Acetaminophen.
   D. Aspirin.

5. Which is most appropriate to add at this time?
   A. Intravenous 0.9% sodium chloride.
   B. Hydrochlorothiazide.
   C. Furosemide.
   D. Fluid restriction.

I. ACUTE KIDNEY INJURY OR ACUTE RENAL FAILURE

A. Definitions and Background
   1. AKI is defined as an acute decrease in kidney function or GFR over hours, days, or even weeks and is associated with an accumulation of waste products and (usually) volume.
   2. Criteria and classification of AKI
      a. Definition of AKI according to KDIGO (not graded)
         i. Increase in SCr of 0.3 mg/dL or more within 48 hours; or
         ii. Increase in SCr to 1.5 times baseline or more (baseline known or presumed within prior 7 days); or
         iii. Urinary volume less than 0.5 mL/kg/hour for at least 6 hours
      b. Urinary output classification
         i. Anuric: Less than 50 mL/24 hours; associated with worse outcomes
         ii. Oliguric: Less than 0.5 mL/kg/hour for 12 hours or more
         iii. Nonoliguric: More than 500 mL/24 hours; associated with better patient outcomes and easier to manage because of fewer problems with volume overload
      c. Staging of AKI (Table 1): Can categorize according to risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) categories or into stages 1–3 (Acute Kidney Injury Network [AKIN] AKIN or KDIGO) on the basis of changes in SCr and urinary output
      d. Common complications include fluid overload and acid-base and electrolyte abnormalities.

Table 1. Staging of AKI

RIFLE Classification (2004)			AKIN Criteria (2007)		KDIGO Staging (2012)		Common Criteria
	Classification	**SCr or GFR Criteria**	**Stage**	**SCr**	**Stage**	**SCr**	**Urinary Output**
R	Risk of renal dysfunction	SCr increase to 1.5 × baseline *or* GFR decrease > 25%	1	≥ 0.3-mg/dL increase *or* 1.5–2.0 × baseline	1	≥ 0.3-mg/dL increase *or* 1.5–1.9 × baseline	< 0.5 mL/kg/hr for 6–12 hr
I	Injury to kidney	SCr increase to 2 × baseline *or* GFR decrease > 50%	2	2–3 × baseline	2	2.0–2.9 × baseline	< 0.5 mL/kg/hr for ≥ 12 hr
F	Failure of kidney function	SCr increase to 3 × baseline *or* GFR decrease > 75% *or* SCr ≥ 4 mg/dL with acute rise of > 0.5 mg/dL per table in the consensus guideline	3	> 3 × baseline *or* SCr ≥ 4 mg/dL with an acute increase of ≥ 0.5 mg/dL; *or* on RRT	3	≥ 3 × baseline *or* increase to ≥ 4.0 mg/dL *or* Initiation of RRT *or* in patients < 18 yr, decrease in eGFR to < 35 mL/min/1.73 m^2	< 0.3 mL/kg/hr for ≥ 24 hr *or* Anuria for ≥ 12 hr
L	Loss of kidney function	Complete loss of kidney function for > 4 wk					
E	End-stage kidney disease	Complete loss of kidney function for > 3 mo					

AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease: Improving Global Outcomes; RIFLE = risk, injury, failure, loss, end-stage (stages of AKI); RRT = renal replacement therapy.

Information from: Bellomo R, Ronco C, Kellum JA, et al.; the ADQI Workgroup. Acute renal failure – definition, outcome measures, animal models, and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12; Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.

3. Community-acquired AKI
    a. Low incidence (0.02%) in otherwise healthy patients
    b. As high as 13% incidence among patients with CKD
    c. Usually has a very high survival rate (70%–95%)
    d. Single insult to the kidney, often drug induced
    e. SCr may return to baseline but may lead to development or progression of CKD
4. Hospital-acquired AKI
    a. Has a moderate incidence (2%–5%) and moderate survival rate (30%–50%)
    b. Single or multifocal insults to the kidney
    c. Can still be reversible
5. A 2015 international study of critically-ill patients found AKI in over 50% of intensive care unit patients, with mortality 4–5 times higher than in those without AKI (Int Care Med 2015;41:1411-23).
6. Estimating kidney function in AKI
    a. Difficult because commonly used SCr-based equations (Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD], and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) are not appropriate (assume stable SCr)
    b. Equations by Brater and Jelliffe are probably more accurate than the Cockcroft-Gault equation but have not been rigorously tested.
    c. The Chen formula for kinetic eGFR provides a promising, simple method to estimate kidney function when SCr is not stable. Further study is still needed.
    d. If patient is nonoliguric, can calculate creatinine clearance (CrCl) according to a timed urine collection and using the average of SCr samples obtained before and after the urine collection

B. Risk Factors Associated with AKI
1. Preexisting CKD (eGFR less than 60 mL/minute/1.73 m^2)
2. Volume depletion: Vomiting, diarrhea, poor fluid intake, fever, diuretic use, intravascular or effective volume depletion (e.g., heart failure, liver disease with ascites)
3. Use of nephrotoxic agents or medications
    a. Intravenous radiographic contrast
    b. Aminoglycosides and amphotericin
    c. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors
    d. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)
    e. Cyclosporine and tacrolimus
    f. Combination of piperacillin/tazobactam plus vancomycin (Crit Care Med 2018;46:12-20).
4. Obstruction of the urinary tract

C. Classifications of AKI (Table 2)
1. Prerenal AKI
    a. Initially, the kidney is undamaged.
    b. Characterized by hypoperfusion to the kidney
        i. Systemic hypoperfusion: Hemorrhage, volume depletion, drugs, heart failure
        ii. Isolated kidney hypoperfusion: Renal artery stenosis, emboli
    c. Physical examination: Hypotension, signs of volume depletion
    d. Urinalysis will initially be normal (no sediment) but concentrated.
2. Functional AKI
    a. Kidney is undamaged; often classified as prerenal azotemia
    b. Caused by reduced glomerular hydrostatic pressure; often without hypotension

c. In general, medication-related (cyclosporine, ACEIs and ARBs, and NSAIDs) or seen in patients with low effective blood flow (patients with HFrEF, patients with liver disease, and older adults) who cannot compensate for alterations in afferent and efferent tone
d. Concentrated urine

3. Intrinsic AKI
   a. Kidney is damaged, and damage can be linked to the structure involved: Small blood vessels, glomeruli, renal tubules, and interstitium
   b. Most common cause is ATN; other causes include AIN, vasculitis, and acute glomerulonephritis.
   c. History: Identifiable insult, drug use, infections
   d. Physical examination: Normotensive, euvolemic, or hypervolemic depending on the cause; check for signs of allergic reactions or embolic phenomenon
   e. Urinalysis will reflect damage (e.g., granular casts, epithelial cell casts); urine generally is not concentrated.
4. Postrenal AKI
   a. Kidney is initially undamaged. Bladder outlet obstruction is the most common cause of post-renal AKI. Lower urinary tract obstruction may be caused by calculi. Ureteric obstructions may be caused by clots or intraluminal obstructions. Extrarenal compression can also cause postrenal disease. Elevated intraluminal pressure upstream of the obstruction will result in damage if the obstruction is not relieved.
   b. History: Trauma, benign prostatic hyperplasia, cancers
   c. Physical examination: Distended bladder, enlarged prostate
   d. Urinalysis may be nonspecific.
   e. Radiography or ultrasonography may reveal hydronephrosis and help identify obstruction.

Table 2. Classifications of AKI

	Prerenal and Functional	**Intrinsic (ATN and AIN)**	**Postrenal**
History and clinical presentation	Volume depletion Renal artery stenosis Heart failure Hypercalcemia NSAID, ACEI, and ARB use Cyclosporine	Longstanding renal hypoperfusion Nephrotoxins (e.g., contrast or antibiotics) Vasculitis Glomerulonephritis	Kidney stones BPH Cancers
Physical examination	Hypotension Dehydration Petechia if thrombotic Ascites	Rash, fever (with AIN) Persistent hypotension	Distended bladder Enlarged prostate
Serum BUN/SCr ratio	> 20:1	10–15:1	10–15:1
Urinary sodium	< 20 mEq/L	> 40 mEq/L	> 40 mEq/L
FENa[a]	< 1%	> 2%	> 2%
FeU	< 35%	> 50%	> 50%
Urinary osmolality	High urine osmolality	Low urine osmolality	Low urine osmolality
Urinary sediment	Normal Consider adding Hyaline casts	Muddy brown granular casts; tubular epithelial casts; hyaline casts	Variable; may be normal

Table 2. Classifications of AKI *(continued)*

	Prerenal and Functional	Intrinsic (ATN and AIN)	Postrenal
Urinary WBC	Negative	2–4+	Variable
Urinary RBC	Negative	2–4+	1+
Proteinuria	Negative	Positive	Negative

ACEI = angiotensin-converting enzyme inhibitor; AIN = acute interstitial nephritis; ARB = angiotensin II receptor blocker; ATN = acute tubular necrosis; BPH = benign prostatic hypertrophy; FENa = fractional excretion of sodium; FeU = fractional excretion of urea; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell count.

[a]Calculation of fractional excretion of sodium (FENa − percentage of Na filtered at the glomerulus that is excreted in the urine)

$$\text{FENa (\%)} = \frac{(\text{urinary sodium})/(\text{serum sodium})}{(\text{urinary creatinine})/(\text{SCr})} \times 100$$

D. Prevention of AKI
   1. Avoid nephrotoxic drugs, when possible.
   2. Ensure adequate hydration.
   3. Educate patient.
   4. Use drug therapies to decrease the incidence of contrast-induced nephropathy (see section II, "Drug-Induced Kidney Damage").

E. Treatment and Management of Established AKI
   1. Prerenal azotemia: Correct primary hemodynamics.
      a. Intravenous normal saline, Lactated Ringer solution or other balanced crystalloid, if volume depleted
      b. Blood pressure management, if needed
      c. Blood products, if needed
      d. Hold or discontinue medications that affect renal hemodynamics (i.e., ACEIs, ARBs, NSAIDs).
   2. Intrinsic: No specific therapy universally effective
      a. Eliminate the causative hemodynamic abnormality or toxin.
      b. Avoid additional insults.
      c. Manage fluid and electrolytes to prevent volume depletion or overload and electrolyte imbalances.
      d. Nutrition support is important, but no specific recommendations are widely accepted.
      e. Medical therapy recommendations according to the KDIGO guidelines
         i. Loop diuretics: Recommend not using to prevent AKI (grade 1B) and suggest not using to treat AKI, except to manage hypervolemia (grade 2C)
         ii. Therapeutic agents (e.g., dopamine, nesiritide, fenoldopam, mannitol) are not indicated in AKI management and may be harmful for the patient.
   3. Postrenal AKI: Monitor fluid balance and manage fluid losses from postobstructive diuresis. Early identification is important. Consult urology or radiology.
   4. Indications for renal replacement therapy (RRT) in AKI
      a. BUN greater than 100 mg/dL or signs of uremia (e.g., encephalopathy, pericarditis)
      b. Volume overload unresponsive to diuretics
      c. Life-threatening electrolyte imbalance: Hyperkalemia, hypermagnesemia
      d. Refractory metabolic acidosis

Patient Cases

6. A 67-year-old man is referred for intermittent chest pain. His medical history is significant for CKD KDIGO category G3a, type 2 diabetes, and hypertension. Medications include enalapril, hydrochlorothiazide, and pioglitazone. Laboratory values include SCr 1.8 mg/dL, glucose 189 mg/dL, Hgb 12 g/dL, and hematocrit (Hct) 36%. His physical examination is normal. The treatment plan is elective cardiac catheterization. Which is best for hydration?
   A. 0.9% sodium chloride.
   B. 0.45% sodium chloride.
   C. 5% dextrose/0.45% sodium chloride.
   D. Oral hydration with water.

7. After the administration of radiocontrast, which best represents the optimal time to reevaluate renal function to assess for the development of contrast-associated nephropathy?
   A. 6 hours.
   B. 24 hours.
   C. 4 days.
   D. 7 days.

II. DRUG-INDUCED KIDNEY DAMAGE

A. Introduction: Drugs can cause kidney damage through many mechanisms. Evaluate potential drug-induced nephropathy on the basis of the period of ingestion, patient risk factors, and the propensity of the suspected agent to cause kidney damage.
   1. Risk factors
      a. History of CKD
      b. Advanced age
      c. Critical illness
   2. Epidemiology
      a. 7% of all drug toxicities
      b. 18%–27% of AKI in hospitals
      c. 1%–5% of NSAID users in community
      d. Most implicated medications: Aminoglycosides, NSAIDs, ACEIs, intravenous contrast dye, amphotericin, piperacillin/tazobactam plus vancomycin
   3. The kidneys are at elevated risk of toxic injury because:
      a. High exposure to toxin: Kidney receives 20%–25% cardiac output.
      b. Autoregulation and specialized blood flow through glomerulus
      c. High intrarenal drug metabolism
      d. Tubular transport processes
      e. Concentration of solutes (i.e., toxins) in tubules
      f. High energy requirements of tubule epithelial cells
      g. Urine acidification
   4. Pseudo-nephrotoxicity
      a. Drugs that inhibit the tubular secretion of creatinine: Trimethoprim, cimetidine
      b. Drugs that increase BUN: Corticosteroids, tetracycline
      c. Drugs that interfere with the creatinine assay: Cefoxitin and other cephalosporins

B. Acute Tubular Necrosis
   1. Most common drug-induced kidney disease in the inpatient setting
   2. Aminoglycoside nephrotoxicity
      a. Incidence: 1.7%–58% of patients
      b. Pathogenesis
         i. Caused by proximal tubular damage leading to obstruction of the lumen
         ii. Cationic charge of drug leads to binding to tubular epithelial cells and uptake into those cells.
         iii. Accumulation of phospholipids and toxicity
      c. Presentation
         i. Gradual rise in SCr concentrations and decrease in GFR after 6–10 days of therapy
         ii. Patients usually have nonoliguric kidney failure.
         iii. Wasting of electrolytes (i.e., hypokalemia and hypomagnesemia) may occur.
      d. Risk factors
         i. Related to dosing: Large total cumulative dose, prolonged therapy, trough concentration exceeding 2 mg/L, recent previous aminoglycoside therapy
         ii. Concurrent use of other nephrotoxins (cyclosporine, amphotericin B, diuretics, vancomycin)
         iii. Patient related: Preexisting kidney disease or damage, advanced age, poor nutrition, shock, gram-negative bacteremia, liver disease, hypoalbuminemia, obstructive jaundice, dehydration, and K and magnesium deficiencies
      e. Prevention
         i. Avoid use in high-risk patients.
         ii. Maintain adequate hydration.
         iii. Limit the total cumulative aminoglycoside dose.
         iv. Avoid use of other nephrotoxins.
         v. Use extended-interval (once daily) dosing; monitor these and other high-risk patients closely.
         vi. Close therapeutic drug monitoring is necessary in patients with preexisting kidney disease.
   3. Radiographic contrast media nephrotoxicity related to intravenous contrast use
      a. Incidence
         i. Third leading cause of inpatient AKI
         ii. Less than 2% and up to 50% of patients, depending on risk
         iii. Associated with a high (34%) in-hospital mortality rate
         iv. Commonly used in procedures such as contrast-enhanced computed tomography (CT), cardiac catheterization, angiography, and venography
      b. Pathogenesis
         i. Renal ischemia caused by alteration in intrarenal hemodynamics
            (a) Osmotic diuresis and dehydration. Contrast media based on osmolality:
               (1) High-osmolar contrast media about 2000 mOsm/kg
               (2) Low-osmolar contrast media 600–800 mOsm/kg
               (3) Iso-osmolar contrast media 290 mOsm/kg
            (b) Some contrast agents also cause systemic hypotension on injection and renal vasoconstriction caused by the release of adenosine, endothelin, and other vasoconstrictors.
         ii. Direct tubular toxicity caused by reactive oxygen species; directly influenced by tubular flow rates and duration of exposure of tubules
      c. Presentation
         i. Initial transient osmotic diuresis, followed by tubular proteinuria
         ii. SCr rises within 24 hours and peaks 2–5 days after the procedure.
         iii. 50% of patients develop oliguria, and some will need dialysis.

d. Risk factors for toxicity
    i. Preexisting kidney disease (SCr more than 1.5 mg/dL or eGFR less than 60 mL/minute/1.73 m^2)
    ii. Diabetes mellitus
    iii. Volume depletion
    iv. Age 75 and older
    v. Anemia
    vi. Conditions with decreased blood flow to the kidney (e.g., HFrEF)
    vii. Hypotension
    viii. Other nephrotoxins
    ix. Large doses of contrast (more than 140 mL) or hyperosmolar contrast agents
e. Prevention
    i. Volume expansion with either intravenous isotonic saline or sodium bicarbonate (KDIGO recommendation, grade 1A) beginning 6–12 hours before the procedure; maintain urinary output greater than 150 mL/hour. Recent data analyses from the PRESERVE trial suggested no added benefit on short-term AKI or long-term outcomes from the use of intravenous sodium bicarbonate compared with isotonic saline (N Engl J Med 2018;378:603-14).
    ii. Use an alternative imaging study, if possible.
    iii. Discontinue nephrotoxic agents and avoid diuretics.
    iv. Use low-osmolar or iso-osmolar contrast agents in patients at risk (KDIGO recommendation, grade 1B).
    v. Medications used to prevent contrast-induced nephropathy
        (a) Acetylcysteine: Antioxidant and vasodilatory mechanism. Accumulation of glutathione takes time, so it may not be as effective in emergencies. Various dosing recommendations. Widely used. Considered safe. May use oral acetylcysteine in addition to intravenous hydration (KDIGO suggestion, grade 2D). Recent studies suggest no additional benefit over intravenous hydration (PRESERVE trial: N Engl J Med 2018;378:603-14 and ACT: Circulation 2011;124:1250-9).
        (b) Ascorbic acid: Antioxidant. One large study showed benefit when used immediately before. Not confirmed. Give oral ascorbic acid 3 g before procedure and 2 g twice daily for two doses after procedure. May play a role in emergencies
        (c) Theophylline: Do not use (KDIGO suggestion, grade 2C).
        (d) Fenoldopam: Do not use (KDIGO recommendation, grade 1B).
        (e) Prophylactic hemodialysis (HD) and hemofiltration: Do not use (KDIGO suggestion, grade 2C).
f. Joint Commission standards on medication management regarding radiologic contrast media
    i. Treated as a drug
    ii. Subject to all the standards for medication management in a health system
g. Nephrogenic systemic fibrosis (a.k.a. nephrogenic fibrosing dermopathy)
    i. Rare but associated with gadolinium-based agents used in high doses for magnetic resonance imaging/angiogram
    ii. Occurs in patients with moderate CKD to end-stage renal disease (ESRD) given intravenous contrast, and systemic acidosis seems to be a risk factor
    iii. Although gadolinium does not cause AKI, it is considered inappropriate for use in patients with AKI or CKD.
    iv. Onset 2–18 days after exposure
    v. Presents as burning; itching; swelling, hardening, or tightening of skin; skin patches; spots on eyes; joint stiffness; and muscle weakness

vi. Can cause organ damage, and deaths have occurred
vii. In 2010, the U.S. Food and Drug Administration (FDA) required the addition of a warning to prescribing information.

4. Cisplatin nephrotoxicity
   a. Incidence: 6%–13% with appropriate dosing and administration
   b. Pathogenesis: Complex; direct tubular toxin
   c. Presentation
      i. SCr peaks 10–12 days after therapy begins but may continue to rise with subsequent cycles of therapy.
      ii. Renal magnesium wasting is common (may be severe with central nervous system symptoms) and may be accompanied by hypokalemia and hypocalcemia.
      iii. May result in irreversible kidney damage
   d. Risk factors for toxicity: Many courses of cisplatin, advanced patient age, dehydration, concurrent nephrotoxins, kidney irradiation, alcohol abuse
   e. Prevention
      i. Avoid concurrent use of nephrotoxins.
      ii. Use smallest dose possible and decrease frequency of administration.
      iii. Aggressive intravenous hydration: 1–4 L within 24 hours of high-dose cisplatin
      iv. Amifostine: Cisplatin-chelating agent may be considered in patients at risk of nephrotoxicity
      v. Alternative platinum analogs (i.e., carboplatin or oxaliplatin) can be used in patients at high risk of nephrotoxicity.
5. Amphotericin B nephrotoxicity
   a. Incidence
      i. Increases as cumulative dose increases
      ii. Approaches 80% with cumulative doses of 4 g or more
   b. Pathogenesis
      i. Direct proximal and distal tubular toxicity
      ii. Arterial vasoconstriction
   c. Presentation
      i. Manifests after administration of 2–3 g
      ii. Loss of tubular function leads to electrolyte wasting (especially K^+, Na^+, and Mg^{2+}) and distal tubular acidosis.
      iii. Patients may need substantial K^+ and Mg^{2+} replacement.
      iv. SCr increases and GFR decreases because of a decrease in kidney blood flow from vasoconstriction caused by amphotericin.
   d. Risk factors for toxicity: Existing kidney dysfunction, high average daily doses, diuretic use, volume depletion, concomitant nephrotoxins, rapid infusion
   e. Prevention
      i. Avoid other nephrotoxins (especially cyclosporine) and limit the total cumulative dose.
      ii. Intravenous hydration with 0.9% sodium chloride at least 1 L/day before each dose
      iii. Use a liposomal product in high-risk patients.

C. Functional (Hemodynamically Mediated) AKI
   1. Caused by a decrease in intraglomerular pressure through the vasoconstriction of afferent arterioles or the vasodilation of efferent arterioles
   2. ACEIs and ARBs
      a. Pathogenesis
         i. Vasodilation of the efferent arteriole
         ii. Leads to a decrease in glomerular hydrostatic pressure and a resultant decrease in GFR

b. Presentation
    i. Exerts a predictable dose-related reduction in GFR
    ii. SCr is usually expected to rise by up to 30%.
        (a) Usually occurs within 2–5 days
        (b) Usually stabilizes in 2–3 weeks
        (c) Increases greater than 30% may be harmful.
        (d) Usually reversible on drug discontinuation
c. Risk factors for toxicity: Patients with bilateral (or unilateral with a solitary kidney) renal artery stenosis, decreased effective kidney blood flow (HFrEF, liver disease), preexisting kidney disease, and volume depletion
d. Prevention
    i. Initiate therapy with low doses and gradually titrate.
    ii. Change to long-acting agents once tolerance is established.
    iii. Initially, monitor kidney function and SCr concentrations daily for inpatients and weekly for outpatients.
    iv. Avoid concomitant use of diuretics, if possible, during therapy initiation.
    v. Avoid concomitant use of NSAIDs.

3. NSAIDs
    a. Incidence: Estimates indicate that 500,000–2.5 million people develop NSAID-induced nephrotoxicity annually in the United States.
    b. Pathogenesis
        i. Vasodilatory prostaglandins help maintain glomerular hydrostatic pressure by afferent arteriolar dilation, especially in times of decreased kidney blood flow.
        ii. NSAID administration in the setting of decreased kidney perfusion reduces this compensatory mechanism by decreasing the production of prostaglandins, resulting in afferent vasoconstriction and reduced glomerular blood flow.
    c. Presentation
        i. Can occur within days of starting therapy
        ii. Patients generally have low urinary volume and Na; may also have an increase in BUN, SCr, K^+, edema, and weight
    d. Risk factors for toxicity: Preexisting kidney disease, systemic lupus erythematosus, high plasma renin activity (e.g., HFrEF, liver disease), diuretic therapy, atherosclerotic disease, and advanced age
    e. Prevention
        i. Use therapies other than NSAIDs, when appropriate (e.g., acetaminophen for osteoarthritis).
        ii. COX-2–specific inhibitors have not been shown to cause less kidney dysfunction, and they increase cardiovascular complications.
    f. Treatment
        i. If NSAID-induced AKI is suspected, discontinue drug and give supportive care.
        ii. Avoid concomitant use of medications affecting the renin-angiotensin-aldosterone system.
        iii. Recovery is usually rapid.

4. Cyclosporine and tacrolimus
    a. Incidence
        i. 5-year risk of developing CKD after transplantation of a nonrenal organ is 7%–21%.
        ii. Occurrence of kidney failure in the transplant recipient population increases the risk of death by 4-fold.

b. Pathogenesis
    i. Caused by a dose-related hemodynamic mechanism; calcineurin inhibitors may also cause chronic interstitial nephritis through a separate mechanism that is not dose related
    ii. Causes vasoconstriction of afferent arterioles through possible increased activity of various vasoconstrictors (thromboxane A_2, endothelin, sympathetic nervous system) or decreased activity of vasodilators (nitric oxide, prostacyclin)
    iii. Increased vasoconstriction from angiotensin II may also contribute.
    iv. Effects usually resolve with a dose reduction.
c. Presentation
    i. Can occur within days of starting therapy
    ii. SCr rises and eGFR decreases.
    iii. Patients often have hypertension, hyperkalemia, and hypomagnesemia.
    iv. A biopsy is often needed for kidney transplant recipients to distinguish drug-induced injury from acute allograft rejection.
d. Risk factors for toxicity include advanced age, high initial cyclosporine dose, kidney graft rejection, hypotension, infection, and concomitant nephrotoxins.
e. Prevention
    i. Monitor serum cyclosporine and tacrolimus concentrations closely.
    ii. Use lower doses in combination with other nonnephrotoxic immunosuppressants (e.g., steroids, mycophenolate mofetil).
    iii. Calcium channel blockers *may* help antagonize the vasoconstrictor effects of cyclosporine by dilating afferent arterioles.

D. Tubulointerstitial Disease
1. Involves the renal tubules and the surrounding interstitium
2. Onset can be acute or chronic.
    a. Acute onset generally involves interstitial inflammatory cell infiltrates, rapid loss of kidney function, and systemic symptoms (i.e., fever and rash).
    b. Chronic onset shows interstitial fibrosis, slow decline in kidney function, and no systemic symptoms.
3. Acute allergic interstitial nephritis
    a. Cause of up to 3% of all AKI cases; caused by an allergic hypersensitivity reaction that affects the interstitium of the kidney
    b. Many medications and medication classes can cause this type of kidney failure, including β-lactams and NSAIDs (although the presentations are different).
        i. Penicillins: Classic presentation of acute allergic interstitial nephritis. Signs and symptoms occur about 1–2 weeks after therapy initiation and include fever, maculopapular rash, eosinophilia, pyuria, hematuria, and proteinuria. Eosinophiluria may also be present.
        ii. NSAIDs: Onset much more delayed; typically begins about 6 months into therapy. Usually occurs in older adults receiving chronic NSAID therapy. Patients do not usually have systemic symptoms.
    c. Kidney biopsy may be needed to confirm the diagnosis.
    d. Treatment includes discontinuing the offending agent and possibly initiating steroid therapy.
4. Chronic interstitial nephritis
    a. Often progressive and irreversible
    b. Lithium
        i. Toxicity results from a duration-related decrease in response to antidiuretic hormone after long-term use (more than 10 years of therapy).

ii. Clinical presentation
(a) Often asymptomatic, with slow progression over years
(b) May be recognized by slow increases in blood pressure or BUN and SCr
iii. Risks include long duration of use, elevated serum concentrations, and repeated episodes of AKI from lithium toxicity.
iv. Prevention is accomplished by maintaining the lowest serum lithium concentrations possible, avoiding dehydration, and monitoring kidney function closely.
c. Cyclosporine and tacrolimus: Presents later in therapy (about 6–12 months) than hemodynamically mediated toxicity

5. Papillary necrosis
a. Form of chronic interstitial nephritis affecting the papillae, causing necrosis of the collecting ducts
b. Results from the long-term use of analgesics
i. "Classic" example was with products that contained phenacetin.
ii. Occurs more often with combination products
iii. Products containing caffeine may also increase risk.
c. Evolves slowly as time progresses
d. Affects women more often than men
e. Difficult to diagnose, and much controversy remains about risk, prevention, and cause

E. Postrenal (Obstructive) Nephropathy
1. Results from obstruction of the flow of urine after glomerular filtration
2. Renal tubular obstruction
a. Caused by intratubular precipitation of tissue degradation products or precipitation of drugs or their metabolites
i. Tissue degradation products
(a) Uric acid intratubular precipitation after tumor lysis after chemotherapy
(b) Drug-induced rhabdomyolysis leading to intratubular precipitation of myoglobin
(c) Results in rapid decline in kidney function, with resultant oliguric or anuric kidney failure
ii. Drug precipitation: Sulfonamides, methotrexate, acyclovir, ascorbic acid; needlelike crystals observed in leukocytes found on urinalysis can prompt diagnosis
b. Prevention includes pretreatment hydration, maintenance of high urinary volume, and alkalinization of the urine.
3. Extrarenal urinary tract obstruction
a. Benign prostatic hypertrophy can be worsened by anticholinergics.
b. Bladder outlet or ureteral obstruction from fibrosis after cyclophosphamide for hemorrhagic cystitis
4. Nephrolithiasis
a. Usually does not affect GFR, so does not have the classic signs and symptoms of nephrotoxicity
b. Some medications contribute to the formation of kidney stones: triamterene, sulfadiazine, indinavir, and ephedrine derivatives.

F. Glomerular Disease
1. Proteinuria is the hallmark of glomerular disease and may occur with or without a decrease in GFR.
2. A few distinct drugs can cause glomerular disease.
a. NSAIDs: Associated with acute allergic interstitial nephritis
b. Heroin: Can be caused by direct toxicity or toxicity from additives or infection from injection, and ESRD develops in most cases
c. Parenteral gold: Results from immune complex formation along glomerular capillary loops

III. CHRONIC KIDNEY DISEASE

A. Background
   1. Prevalence: According to the 2020 U.S. Renal Data System Annual Report: 14.9% of the U.S. adult population (20 years and older) in the National Health and Nutrition Examination Survey (2015–2018) had CKD. There were 554,038 patients on dialysis in 2018 and 229,887 transplant recipients. Incidence rate is flat, so growth in the number of patients with ESRD results mainly from the longer life span of these patients.
   2. Definition of CKD
      a. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), CKD is kidney damage for more than 3 months, as defined by structural or functional abnormality of the kidney, with or without decreased GFR. Manifested by either pathologic abnormalities or markers of kidney damage – including albuminuria, abnormal urine sediment, serum electrolyte abnormalities, abnormal histology, or abnormalities in imaging tests – *or* GFR less than 60 mL/minute/1.73 m^2 for 3 months, with or without kidney damage (Table 3)

Table 3. KDOQI Stages in CKD

Stage of Renal Disease	Damage	GFR (mL/min/1.73 m^2)
Increased risk of developing kidney disease	Risk factors for CKD (diabetes, HTN, family history)	≥ 90
Stage 1	Kidney damage with normal GFR	≥ 90
Stage 2	Kidney damage with mild decrease in GFR	60–89
Stage 3	Moderate decrease in GFR	30–59
Stage 4	Severe decrease in GFR	15–29
Stage 5	Kidney failure	< 15

CKD = chronic kidney disease; HTN = hypertension.

      b. According to the KDIGO clinical practice guideline for the evaluation and management of CKD, CKD is defined as abnormalities in kidney structure or function for more than 3 months. These abnormalities may be seen as persistent markers of kidney damage or GFR less than 60 mL/minute/1.73 m^2 (Table 4).

Table 4. KDIGO Categories in CKD

GFR Category	Terms	GFR (mL/min/1.73 m^2)
G1	Kidney damage with normal or high GFR	≥ 90
G2	Kidney damage with mildly decreased GFR	60–89
G3a	Mildly to moderately decreased GFR	45–59
G3b	Moderately to severely decreased GFR	30–44
G4	Severely decreased GFR	15–29
G5	Kidney failure	< 15

B. Etiology
   1. Diabetes (45% of new cases of ESRD in the United States)
   2. Hypertension (28% of new cases)
   3. Glomerulonephritis (7.4%)
   4. Others: Urinary tract disease, polycystic kidney disease, lupus, analgesic nephropathy, unknown

C. Risk Factors
   1. Susceptibility (associated with an increased risk but not proven to cause CKD): Advanced age, reduced kidney mass, low birth weight, racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia; mostly not modifiable
   2. Initiation (directly cause CKD): Diabetes, hypertension, autoimmune disease, polycystic kidney diseases, and drug toxicity; may be modifiable by drug therapy
   3. Progression (result in faster decline in kidney function): Hyperglycemia, elevated blood pressure, proteinuria, and smoking

Patient Cases

Questions 8–11 pertain to the following case.

A 55-year-old man has a history of hypertension and newly diagnosed type 2 diabetes. He denies alcohol use but does smoke cigarettes (1 pack/day). His medications include atenolol 50 mg/day and a multivitamin. At your pharmacy, his blood pressure is 149/92 mm Hg. His ACR is 400 mg/g. A recent SCr is 1.9 mg/dL, which is consistent with a value measured 3 months earlier. His eGFR is 50 mL/minute/1.73 m^2.

8. Which category best reflects his kidney disease, according to the KDIGO criteria?
   A. G2.
   B. G3a.
   C. G3b.
   D. G4.

9. Using the KDIGO categorization, which best assesses this patient's albuminuria?
   A. Category A1.
   B. Category A2.
   C. Category A3.
   D. Nephrotic-range proteinuria.

10. Assuming that nonpharmacologic approaches have been optimized, which is best to limit the progression of his kidney disease?
   A. Add nifedipine.
   B. Add diltiazem.
   C. Add enalapril.
   D. Increase atenolol.

11. Enalapril is added to this patient's regimen. Two weeks later, he returns for a follow-up. His blood pressure is 139/89 mm Hg. A repeat SCr is 2.3 mg/dL, and serum potassium is 5.2 mEq/L. Which is the best recommendation for this patient?
   A. Add chlorthalidone 50 mg/day. Monitor blood pressure, SCr, and K in 2 weeks.
   B. Change enalapril to diltiazem extended release. Monitor blood pressure, SCr, and K in 2 weeks.
   C. Change enalapril to valsartan.
   D. Increase atenolol.

Patient Cases *(Cont'd)*

12. A study compared use of an ARB alone and in combination with an ACEI in patients with CKD. Acute kidney injury occurred in 80 of 724 patients (11%) receiving monotherapy and 130 of 724 patients (18%) receiving combination therapy. Given this information, which most accurately depicts the number of patients needed to harm?

    A. 7.

    B. 14.

    C. 50.

    D. 105.

D. Albuminuria or Proteinuria

1. Marker of kidney damage, progression factor, and cardiovascular risk factor. Can be classified as in Table 5

Table 5. KDIGO Categories of Albuminuria

Category	Classification	ACR (mg/g)	Daily Excretion (mg/24 hr)
A1	Normal to mildly increased	< 30	< 30
A2	Moderately increased	30–300	30–300
A3	Severely increased albuminuria	> 300	> 300
	Nephrotic-range proteinuria		> 3000

ACR = albumin/creatinine ratio.

2. Assessment for proteinuria: Usually assessed by measuring urinary ACR. Spot urine: Untimed sample is adequate for adults and children (screening test). A timed (24-hour) urine collection may be used to quantify severe proteinuria.

E. Assessment of Kidney Function

1. Serum creatinine (SCr)
    a. Avoid use as the sole assessment of kidney function.
    b. Depends on age, sex, weight, and muscle mass
    c. All laboratories now use "standardized" SCr traceable to isotope dilution mass spectrometry, which decreases variability in results between laboratories.
2. Measurement of GFR: Inulin, iothalamate, and others are very rarely used in clinical practice.
3. Measurement of CrCl through urine collection
    a. Reserve for vegetarians, patients needing dietary assessment, or those with abnormal muscle mass (e.g., patients with low muscle mass, patients with amputations) or when documenting the need to start or continue dialysis.
    b. Urine collection yields a better estimate in patients with very low muscle mass.
    c. In most cases, equations overestimate kidney function because SCr concentrations are low in patients with very low muscle mass.

4. Estimated CrCl using the Cockcroft-Gault equation (mL/minute): Overestimates GFR because of tubular secretion of creatinine

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{body weight}}{\text{SCr} \times 72} \ (\times 0.85 \text{ if female})$$

Although actual body weight was used in the original publication, either ideal body weight or adjusted body weight is often used instead.

5. eGFR with MDRD study data equation
   a. eGFR (mL/minute/1.73 m^2) in patients with known CKD (not accurate in patients with a GFR greater than 60 mL/minute/1.73 m^2 or less accurate in patient populations without kidney disease)
   b. Isotope dilution mass spectrometry–traceable four-variable MDRD formula correlates well with the original MDRD formula; simpler to use:

$$\text{eGFR (mL/minute/1.73 m}^2\text{)} = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \ (\times 0.742 \text{ if female}) \ (\times 1.212 \text{ if African American})$$

   c. This equation is available at www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx or www.kidney.org.
6. CKD-EPI equation: Alternative equation based on sex, SCr, serum cystatin C, and age. This equation was updated in 2021 to no longer include race. More accurate than MDRD at GFR values greater than 60 mL/minute/1.73 m^2. Available at https://www.kidney.org/professionals/kdoqi/gfr_calculator.
7. For children, use the modified Schwartz "bedside" formula; see https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/children-conventional-unit/Pages/default.aspx.

F. Diabetic Kidney Disease
   1. Pathogenesis
      a. Hypertension (systemic and intraglomerular)
      b. Glycosylation of glomerular proteins
      c. Genetic links
   2. Diagnosis
      a. Long history of diabetes
      b. Proteinuria
      c. Retinopathy often coexists, suggestive of microvascular disease.
   3. Monitoring
      a. Type 1 diabetes: Begin annual monitoring for albuminuria 5 years after diagnosis.
      b. Type 2 diabetes: Begin annual monitoring for albuminuria immediately (do not know how long patient has had diabetes mellitus).
      c. Monitor albuminuria twice annually if ACR is greater than 300 mg/g and/or estimated eGFR is 30–60 mL/min/1.73 m^2.

4. Management and slowing progression
    a. Aggressive blood pressure management (Table 6)

Table 6. Goal Blood Pressure Readings in Patients with Diabetes

Group	Goal Blood Pressure (maximum)	Level of Evidence
ADA 2022	140/90 mmHg[a]	
KDIGO 2021	SBP < 120 mmHg	2B
ACC/AHA 2017	130/80 mmHg	SBP: B DBP: C

[a]Lower blood pressure targets (e.g., < 130/80 mmHg) should be considered in some patients based on anticipated risks and benefits.

ACC/AHA = American College of Cardiology/American Heart Association; ADA = American Diabetes Association; DBP = diastolic blood pressure; SBP = systolic blood pressure.

        i. Either ACEIs or ARBs are preferred and should be used with any degree of proteinuria, even if the patient is not hypertensive.
            (a) Use moderate to high doses with proteinuria.
            (b) Hold ACEI or ARB if serum potassium is greater than 5.6 mEq/L or if SCr increases by more than 30% after initiation. Potassium binders such as patiromer or sodium zirconium cyclosilicate can be considered for chronic management of hyperkalemia.
            (c) Increased risk of hyperkalemia if combined with direct renin inhibitor
        ii. Most patients will need diuretic in combination (thiazide with stages 1–3 and loop diuretics in stages 4 and 5). Begin a two-drug regimen if blood pressure is greater than 20 mmHg above goal.
        iii. Calcium channel blockers (nondihydropyridine) are second line to ACEIs and ARBs. Data are emerging for combined therapy.
        iv. Dietary sodium consumption should be less than 2.4 g/day. Modify the Dietary Approaches to Stop Hypertension (DASH) diet to limit K intake as well.
    b. Intensive blood glucose control. Glycosylated hemoglobin (A1C) less than 7%. Less aggressive with more advanced CKD
        i. Consider the use of sodium-glucose cotransporter 2 inhibitors in adults with type 2 diabetes and estimated GFR greater than 25 mL/min/1.73 m^2 and ACR greater than 300 mg/g.
    c. Protein restriction: Data are insufficient in adults with diabetes, but 0.8 g/kg/day may slightly reduce progression in stage 4 or 5 CKD and decrease the risk of ESRD. Patients should avoid high-protein diets (greater than 1.3 g/kg/day).
    d. For patients with CKD who are at increased risk for cardiovascular events, progression of CKD, or unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (MRA) is recommended.
        i. Finerenone is a nonsteroidal MRA indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD associated with type 2 diabetes.

G. Nondiabetic Nephropathy
   1. Management of hypertension
      a. 2021 KDIGO Guidelines recommend a goal systolic blood pressure less than 120 mmHg, regardless of severity of albuminuria.
      b. Initial treatment with ACEI or ARB, but not both (see Table 7)

Table 7. KDIGO 2021 Guidelines on Management of Hypertension in CKD

Subgroup	Recommendation	Level of Evidence
Severely increased albuminuria (G1–G4, A3)	Recommend ACEI or ARB	1B
Moderately increased albuminuria (G1–G4, A2)	Suggest ACEI or ARB	2C
No albuminuria	ACEI or ARB may be reasonable	

      c. Combination therapy with thiazide-like diuretics and/or calcium channel blockers may be necessary to achieve blood pressure goals. Avoid combination therapy with direct renin inhibitors.
      d. ACEI or ARBs should be used at the highest tolerable doses.
      e. Blood pressure, serum potassium, and SCr should be monitored within 2–4 weeks of initiation or dosage increase.
      f. Before adjusting ACEI or ARB therapy because of hyperkalemia, attempts should be made to modify dietary potassium intake; discontinue potassium supplements, salt substitutes, or other drugs known to cause hyperkalemia or add potassium-wasting diuretics or oral potassium binders.
      g. The use of sodium–glucose cotransporter 2 inhibitors may also have a role in nondiabetic nephropathy. Dapagliflozin is indicated as an adjunctive agent for use in CKD in patients with persistently elevated urine albumin-to-creatinine ratio (200–5000 mg/g) who are receiving first line therapies.

H. Other Guidelines to Slow Progression
   1. Hyperlipidemia
      a. Assessment
         i. Newly identified CKD: Recommend evaluation of lipid profile (KDIGO, grade 1C) (Table 8).
         ii. Follow-up measurement of lipid concentrations not necessary for most patients (not graded)
      b. Treatment recommendations: Treatment and intensity of therapy is primarily based on ASCVD risk assessment. See Table 8 for 2013 KDIGO recommendations.

Table 8. 2013 KDIGO Lipid Treatment Guidelines

Target Group	Treatment Recommendation	Grade
Adults ≥ 50 yr, GFR category G1–G2	Statin	1B
Adults ≥ 50 yr, GFR category G3a–G5	Statin or statin/ezetimibe	1A
Adults 18–49 yr with CKD before dialysis or transplant with CAD, diabetes, stroke, or estimated risk of coronary death or MI > 10%	Statin	2A
Adults on therapy when dialysis initiated	Continue statin or statin/ezetimibe	2C
Adults with dialysis-dependent CKD	Do *not* start therapy	2A
Adult kidney transplant recipients	Statin	2A

CAD = coronary artery disease; MI = myocardial infarction.

Information from: Wanner C, Tonelli M; KDIGO Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303-9.

   2. Smoking cessation

Patient Cases

13. A 70-year-old man is being assessed for HD access. He has a history of diabetes mellitus and hypertension but is otherwise healthy. Which HD access modality is best to use in this patient?
    A. Subclavian catheter.
    B. Tenckhoff catheter.
    C. Arteriovenous graft.
    D. Arteriovenous fistula.

14. A patient undergoing long-term HD has intradialytic hypotension. After nonpharmacologic approaches have been optimized, which medication is best to manage his low blood pressure?
    A. Levocarnitine.
    B. Sodium chloride tablets.
    C. Fludrocortisone.
    D. Midodrine.

15. A patient with CKD on peritoneal dialysis presents with fever and abdominal pain. She also notes that her peritoneal dialysate has become cloudy. Laboratory evaluation of dialysate reveals many white blood cells, primarily neutrophils. Gram stain and culture of the fluid are ordered. According to the 2016 International Society for Peritoneal Dialysis Peritonitis Recommendations, which is the best empiric therapy for this patient?
    A. Intravenous metronidazole plus gentamicin.
    B. Intravenous clindamycin plus vancomycin.
    C. Cefazolin plus ceftazidime instilled intraperitoneally.
    D. Vancomycin instilled intraperitoneally.

IV. RENAL REPLACEMENT THERAPY

A. Indications for RRT
    1. A: Acidosis (not responsive to bicarbonate)
    2. E: Electrolyte abnormality (hyperkalemia, hyperphosphatemia)
    3. I: Intoxication (boric acid, ethylene glycol, lithium, methanol, phenobarbital, salicylate, theophylline)
    4. O: Fluid overload (symptomatic [pulmonary edema])
    5. U: Uremia (pericarditis and weight loss)

B. Two Primary Modes of Dialysis
    1. Hemodialysis: Most common modality in United States
    2. Peritoneal dialysis

C. Hemodialysis (intermittent for ESRD)
    1. Access
        a. Arteriovenous fistula: Preferred access
            i. Natural, formed by anastomosis of artery and vein
            ii. Lowest incidence of infection and thrombosis, lowest cost, longest survival
            iii. Fistula maturation often takes weeks or months to establish adequate blood flow.

b. Arteriovenous graft
    i. Usually synthetic (polytetrafluoroethylene)
    ii. Often used in patients with vascular disease
c. Catheters
    i. Commonly used if permanent access unavailable
    ii. Problems include high infection and thrombosis rates. Low blood flow leads to inadequate dialysis.

2. Dialysis membranes
    a. Conventional: Not often used anymore. Small pores, smaller surface area
    b. High flux (large pores) and high efficiency (large surface area). Can remove drugs that were impermeable to standard membranes (vancomycin). Large amounts of fluid removed (ultrafiltrate)
3. Adequacy
    a. Kt/V: Unitless parameter. K = clearance, t = time on dialysis, and V = volume of distribution of urea. KDOQI set a minimum of 1.2 (target Kt/V of 1.4).
    b. URR: Urea reduction ratio. URR = [(preBUN – postBUN)/preBUN] × 100%. Goal URR is greater than 65% (target URR of 70%).
4. Common complications of HD
    a. Intradialytic
        i. Hypotension: Related primarily to fluid removal. Common in older adults and in people with diabetes mellitus
            (a) Acute treatment: Trendelenburg position, decrease ultrafiltration rate; administer saline boluses
            (b) Prevention: Accurately set "dry weight"; limit fluid gains between sessions; midodrine 2.5–10 mg orally before dialysis
            (c) Less well-studied agents include fludrocortisone, selective serotonin reuptake inhibitors
        ii. Cramps: Vitamin E 400 international units at bedtime
        iii. Nausea and vomiting
        iv. Headache, chest pain, or back pain
    b. Vascular access complications: Most common with catheters
        i. Infection: *Staphylococcus aureus* is the most common organism. Need to treat aggressively. May need to remove catheter
        ii. Thrombosis: Suspected with low blood flow. Oral antiplatelet agents for prevention not used because of lack of efficacy. Can treat with alteplase 2 mg or reteplase 0.4 unit per lumen; allow to dwell and try to aspirate after 30 minutes; may repeat dose if needed
5. Factors that affect the efficiency of HD
    a. Type of dialyzer used (changes in membrane surface area and pore size)
    b. Length of therapy
    c. Dialysis flow rate
    d. Blood flow rate

D. Continuous RRT for Critically Ill Patients with AKI
1. Continuous venovenous hemofiltration (CVVH): Removes fluid and solutes by convection rather than by diffusion
    a. Drug removal depends on ultrafiltrate production rate and protein binding of drug. Predict drug removal by the sieving coefficient (SC):

$$SC = \frac{\text{concentration of drug in ultrafiltrate}}{\text{concentration of drug in blood}}$$

    b. Requires replacement fluid because of high ultrafiltration rate

2. Continuous venovenous hemodialysis (CVVHD): Dialysate flows countercurrent to blood flow, and solute is removed by diffusion.
3. Continuous venovenous hemodiafiltration (CVVHDF): Ultrafiltration and dialysis; solute is removed by both convection and diffusion. Requires both replacement fluid and dialysate

E. Peritoneal Dialysis
1. Peritoneal dialysis membrane is 1–2 m^2 (approximates the body surface area) and consists of the vascular wall, the interstitium, the mesothelium, and the adjacent fluid films. 1.5–3 L of peritoneal dialysate fluid may be instilled in the peritoneum (fill) by a catheter, allowed to dwell for a specified time, and then drained.
2. Solutes and fluid diffuse across the peritoneal membrane.
3. Peritoneal dialysis is usually *not* used to treat AKI in adults.
4. Types of peritoneal dialysis
   a. Continuous ambulatory peritoneal dialysis: Classic. Requires mechanical process, which requires many manual exchanges throughout the day. Can disrupt daytime routine
   b. Automated peritoneal dialysis: Many variants exist, but continuous cycling peritoneal dialysis is the most common. Patient undergoes many exchanges during sleep by a cycling machine. May have one or two dwells during day. Minimizes potential contamination. Lowest incidence of peritonitis
5. Complications of peritoneal dialysis
   a. Peritonitis – Infection of the peritoneal cavity
      i. Patient technique and population variables influence the infection rate. Older adults or those with diabetes have a higher infection rate. Peritonitis is a main cause of failure of peritoneal dialysis.
      ii. Diagnosis: At least two of the following:
         (a) Clinical features consistent with peritonitis (i.e., abdominal pain and/or cloudy dialysis effluent)
         (b) Dialysis effluent WBC greater than 100/mm^3 or greater than 0.1×10^3 cells/m^3 (after a dwell time of at least 2 hours) with greater than 50% polymorphonuclear leukocytes
         (c) Positive dialysis effluent culture (International Society for Peritoneal Dialysis [ISPD] guideline, 1C)
      iii. Patients on peritoneal dialysis presenting with cloudy effluent can be presumed to have peritonitis and can be treated as such until diagnosis can be confirmed or excluded (ISPD guideline, 1C).
      iv. Etiologic organisms: Most common gram-positive organisms include *Staphylococcus epidermis*, *S. aureus*, and streptococci. Most common gram-negative organisms include *Escherichia coli* and *Pseudomonas aeruginosa*.
      v. Treatment based on ISPD guidelines
         (a) Empiric treatment should cover gram-positive and gram-negative bacteria.
         (b) Vancomycin or a first-generation cephalosporin is administered to cover gram-positive organisms, and a third-generation cephalosporin, an aminoglycoside, or aztreonam is added to cover gram-negative organisms. Intraperitoneal administration is preferred unless the patient has another systemic site of infection.
         (c) Adjust as needed on the basis of culture and sensitivity.
   b. Catheter exit-site infections
      i. Recommended that daily topical application of antibiotic (mupirocin or gentamicin) cream or ointment be applied to catheter exit site for prophylaxis. (ISPD guideline, 1B)
      ii. Prompt treatment of exit-site or catheter tunnel infection is recommended to reduce subsequent peritonitis risk (ISPD guideline, 1C).
   c. Hyperglycemia
   d. Fluid overload

e. Electrolyte abnormalities: Hypercalcemia, hypocalcemia
f. Malnutrition: Hypoalbuminemia
g. Hernia

Patient Case

Questions 16 and 17 pertain to the following case.

A 60-year-old patient on HD has had ESRD for 10 years. His HD access is a left arteriovenous fistula. He has a history of hypertension, coronary artery disease, mild HFrEF, type 2 diabetes, and a seizure disorder. Medications are as follows: epoetin alfa 14,000 units intravenously three times/week at dialysis, a renal multivitamin once daily, atorvastatin 20 mg/day, insulin, calcium acetate 2 tablets three times daily with meals, phenytoin 300 mg/day, and intravenous iron 100 mg/month. Laboratory values are as follows: Hgb 10.2 g/dL, PTH 800 pg/mL, Na 140 mEq/L, K 4.9 mEq/L, SCr 7.0 mg/dL, calcium 9.5 mg/dL, albumin 2.5 g/dL, and phosphorus 7.8 mg/dL. Serum ferritin is 550 ng/mL, and TSAT is 32%. The red blood cell count indices are normal. His WBC is normal, and he is afebrile.

16. Which is most likely contributing to this patient's relative epoetin resistance?
    A. Hyperparathyroidism.
    B. Iron deficiency.
    C. Phenytoin therapy.
    D. Infection.

17. In addition to diet modification and emphasizing adherence, which is best for managing this patient's hyperparathyroidism?
    A. Increase calcium acetate.
    B. Change calcium acetate to sevelamer and add cinacalcet.
    C. Hold calcium acetate and add intravenous vitamin D analog.
    D. Add intravenous vitamin D analog.

V. MANAGING THE COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A. Anemia
    1. Several factors are responsible for anemia in CKD: Decreased erythropoietin production (most important), shorter life span of red blood cells, blood loss during dialysis, iron deficiency, anemia of chronic disease, and renal osteodystrophy
    2. Prevalence: 26% of patients with a GFR greater than 60 mL/minute/1.73 m^2 have anemia, compared with 78% of patients with a GFR less than 15 mL/minute/1.73 m^2.
    3. Signs and symptoms: Similar to those of anemia associated with other causes
    4. Treatment: Treatment of anemia in CKD can decrease morbidity and mortality, reduce left ventricular hypertrophy, increase exercise tolerance, and increase quality of life.
    5. Studies suggest that treatment with erythropoiesis-stimulating agents (ESAs) to high Hgb concentrations (greater than 13 g/dL) increases cardiovascular events. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), for example, failed to show a benefit in outcomes, but treatment with ESAs was associated with increased stroke (N Engl J Med 2009;361:2019-32). This supported earlier data from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial (N Engl J Med 2006;355:2085-98) and the Cardiovascular Risk Reduction by Early Anemia Treatment with epoetin beta (CREATE) trial (N Engl J Med 2006;355:2071-84).

a. Anemia workup: Initiate evaluation when CrCl is less than 60 mL/minute/1.73 m^2 *or* when Hgb is less than 13 g/dL (men) or less than 12 g/dL (women).
   i. Hgb and Hct monitoring recommendations (Table 9)

Table 9. Frequency of hemoglobin (Hgb) and Hematocrit (Hct) monitoring for patients at various stages of CKD

Stage of CKD	Frequency of Monitoring
3	At least annually
4 and 5 (non-dialysis)	At least twice per year
5 (dialysis)	At least every 3 mo

   ii. Mean corpuscular volume
   iii. Reticulocyte count
   iv. Iron studies
      (a) TSAT (serum iron/total iron-binding capacity × 100): Assesses available iron
      (b) Ferritin: Measures stored iron
   v. Serum vitamin B_{12} and folate concentrations
   vi. Stool guaiac

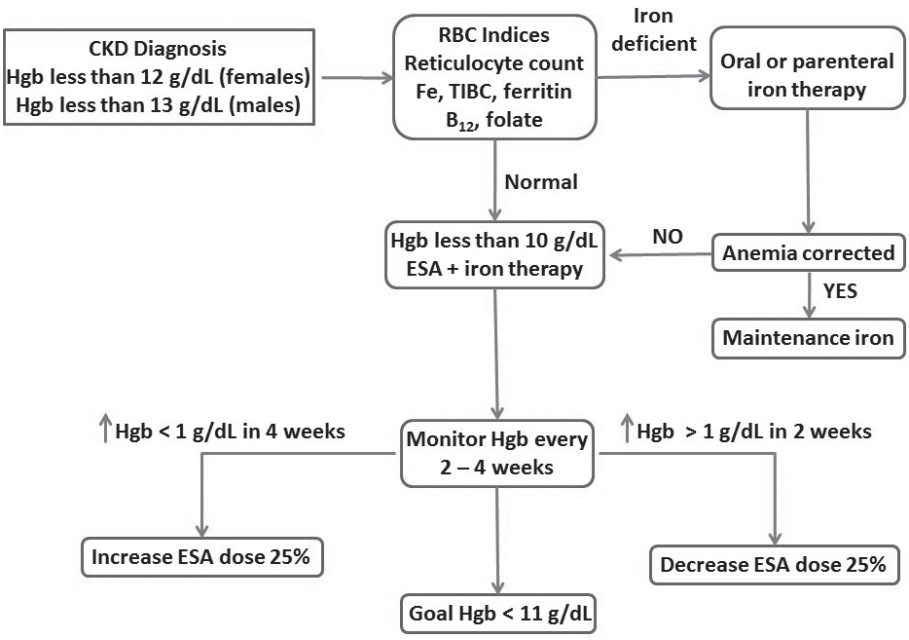

Figure 1. Management of anemia of CKD according to KDIGO and KDOQI guidelines.
CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; Fe = iron; Hb = hemoglobin; RBC = red blood cell; TIBC = total iron-binding capacity.

b. ESAs
   i. Initiation
      (a) Patients with CKD (non-dialysis): Not to be initiated if Hgb is greater than 10 g/dL unless symptomatic. If Hgb is less than 10 g/dL, consider the rate of decline in Hgb and the need to reduce the likelihood of transfusion (particularly in patients who may receive a renal transplant).

(b) Patients with CKD (dialysis): Initiate therapy for Hgb less than 10 g/dL (KDIGO guidelines recommend avoiding an Hgb decrease below 9 g/dL)
(c) Use with caution, if at all, in patients with a history of stroke or cancer (evidence for increased risk of stroke is stronger in patients with nondialysis-dependent CKD compared with the risk in patients on dialysis.).
(d) Iron stores should be replaced before initiating ESAs.
(e) Additional contraindications include uncontrolled hypertension and hypersensitivity reactions.

ii. Maintenance of ESAs: Individualize dosing, and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions; adjust dosing as appropriate.
iii. Epoetin alfa (Epogen, Procrit)
(a) Same molecular structure as human erythropoietin (recombinant DNA technology)
(b) Binds to and activates erythropoietin receptor
(c) Administered subcutaneously or intravenously
(d) Starting dose: 50–100 units/kg three times per week
(e) Subcutaneous dosage requirement is typically 30% less than intravenous dosage requirement.
iv. Darbepoetin alfa (Aranesp)
(a) Molecular structure of human erythropoietin has been modified from 3 *N*-linked carbohydrate chains to 5 *N*-linked carbohydrate chains; increased duration of activity
(b) The advantage is less-frequent dosing (e.g., once weekly, once every 2–3 weeks).
(c) Starting dose:
(1) Non-dialysis CKD: 0.45 mcg/kg once every 4 weeks
(2) Dialysis CKD: 0.45 mcg/kg once per week or 0.75 mcg/kg every 2 weeks
(d) Binds to and activates erythropoietin receptor
(e) May be administered subcutaneously or intravenously
v. Methoxy polyethylene glycol-epoetin beta (Mircera)
(a) Molecular structure of human erythropoietin has been modified through the formation of a chemical bond with methoxyl polyethylene glycol butanoic acid; increased duration of action
(b) Onset of Hgb increase occurs 7–15 days after initial dose.
(c) Less-frequent dosing; initial dose 0.6 mcg/kg body weight once every 2 weeks
(d) Once Hgb stabilizes, can double the dose and administer once monthly
(e) Binds to and activates erythropoietin receptor
(f) May be administered subcutaneously or intravenously

c. Therapy goals
i. Use the lowest possible dose of ESA to prevent blood transfusion.
ii. In non-dialysis patients with CKD, hold or reduce the dose when Hgb is greater than 10 g/dL.
iii. In dialysis patients, hold or reduce the dose when Hgb is greater than 11 g/dL (KDIGO suggests an upper limit of 11.5 g/dL).
iv. Do not exceed an Hgb greater than 13 g/dL.

d. ESA dose adjustment is based on Hgb response.
i. Adjustment parameters are similar for epoetin alfa and darbepoetin alfa.
ii. Maximal increase in Hgb is about 1 g/dL every 2–4 weeks.
iii. Dosages should not be titrated more often than every 4 weeks.
iv. In general, dose adjustments are made in 25% increments (i.e., dosages titrated or tapered by 25% according to current dose).

e. ESA monitoring (Table 10)
   i. Hgb every 2–4 weeks during initiation phase. In maintenance phase of therapy, monitor Hgb at least monthly in dialysis patients and at least every 3 months in non-dialysis patients with CKD.
   ii. Monitor blood pressure because it may rise (treat as necessary).
   iii. Iron stores

Table 10. KDOQI and KDIGO Iron Status Goals

Laboratory Value	KDOQI	KDIGO
TSAT	> 20%	> 30%
Ferritin	> 100 ng/mL (non-dialysis CKD; PD) > 200 ng/mL (HD CKD)	> 500 ng/mL

HD = hemodialysis; PD = peritoneal dialysis.

Information from: KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target; Am J Kidney Dis 2007;50:471-530. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279.

f. Common causes of inadequate response to ESA therapy
   i. Iron deficiency is the most common cause of erythropoietin resistance; however, increased use of intravenous iron products has reduced this problem.
   ii. Infection and inflammation
   iii. Other causes include chronic blood loss, hyperparathyroidism, aluminum toxicity, folate or vitamin B_{12} deficiency, malignancies, malnutrition, hemolysis, and vitamin C deficiency.

g. Iron therapy
   i. Oral iron is not recommended in patients with CKD on dialysis, but a 1- to 3-month trial may be done in predialysis patients with CKD requiring iron therapy.
   ii. Ferric citrate is FDA approved as a phosphate binder and may be useful for oral iron supplementation in patients with CKD not requiring dialysis.
   iii. Most patients with CKD who are receiving ESAs need parenteral iron therapy (increased requirements, decreased oral absorption).
   iv. For adult patients who undergo dialysis, an empiric cumulative or total dose of 1000 mg is usually given, and equations are rarely used.
   v. Monitor TSAT and ferritin as noted every 3 months.
   vi. Adverse effects
      (a) Anaphylactic-type reactions with iron dextran necessitate test dose. Hypersensitivity reaction may occur with all parenteral iron products.
      (b) Hypotension with administration of sodium ferric gluconate, iron sucrose, and ferumoxytol. Monitor during and up to 30 minutes after administration.
      (c) Hypertension. Transient increases in blood pressure occur with ferric carboxymaltose.
      (d) Bloodstream or other serious infections may be worsened by intravenous iron. In these circumstances, it may be appropriate to administer an ESA without repleting iron.

vii. Seven commercial parenteral iron preparations are approved in the United States (Table 11).

Table 11. Parenteral Iron Therapy

Iron Product	Replacement Therapy (TSAT < 30% and ferritin < 500 ng/mL)	Maintenance Therapy (iron stores in goal)	Initial Test Dose
Iron dextran (high-molecular-weight iron dextran: Dexferrum) (low-molecular-weight iron dextran: INFeD)	100 mg IV three times/wk during HD × 10 doses (1 g)	25–100 mg/wk IV × 10 wk	Yes; 25 mg one-time test dose
Sodium ferric gluconate complex (Ferrlecit and generic)	125 mg IV three times/wk during HD × 8 doses (1 g)	31.25–125 mg/wk IV × 10 wk	None needed
Iron sucrose (Venofer)	100 mg IV three times/wk during HD × 10 doses (1 g) For non-HD CKD, 200 mg IV × 5 doses	25–100 mg/wk IV × 10 wk	None needed
Ferumoxytol (Feraheme)	510 mg at up to 30 mg/s, followed by a second 510-mg IV dose 3–8 days later (all CKD)	N/A	None needed
Ferric carboxymaltose (Injectafer)	15 mg/kg IV up to 750 mg; may repeat after at least 7 days (maximum 1500 mg of elemental iron per two-dose course)	N/A	None needed

IV = intravenous(ly); N/A = not applicable; NS = normal saline solution.

B. CKD–Mineral and Bone Disorder (CKD-MBD)
   1. Pathophysiology: Calcium and phosphorus homeostasis is complex, involving the interplay of hormones affecting the bone, gastrointestinal (GI) tract, kidneys, and parathyroid gland. The process may begin as GFR decreases to less than 60 mL/minute/1.73 m^2. The consequences of CKD-MBD include renal osteodystrophy and vascular calcification. Factors contributing to CKD-MBD include the following:
      a. Hyperphosphatemia
      b. Decreased production of 1,25-dihydroxyvitamin D_3
      c. Reduced absorption of calcium in the gut
      d. Decreased ionized (free) calcium concentrations
      e. Direct stimulation of parathyroid hormone (PTH) secretion
      f. Elevated PTH concentrations cause decreased reabsorption of phosphorus and increased reabsorption of calcium in the proximal tubule. This adaptive mechanism is lost as GFR decreases below 30 mL/minute/1.73 m^2. Important: Calcium is not well absorbed through the gut at this point, and calcium concentrations are maintained by increased bone resorption through elevated PTH. Unabated calcium loss from the bone results in renal osteodystrophy.
   2. Prevalence
      a. Main cause of morbidity and mortality in patients undergoing dialysis
      b. Very common
   3. Signs and symptoms
      a. Insidious onset: Patients may experience fatigue and musculoskeletal and GI pain; calcification may be visible on radiography; bone pain and fractures can occur if progression is left untreated.

b. Laboratory abnormalities (Table 12)
    i. Phosphorus
    ii. Corrected calcium (measured calcium + 0.8[4 – serum albumin])
    iii. Parthyroid hormone (PTH)
    iv. Alkaline phosphatase
    v. 25-hydroxyvitamin D

Table 12. KDIGO Guidelines for Frequency of Laboratory Monitoring in Stage 3–5 CKD[a]

	G3a–G3b CKD	G4 CKD	G5–G5D CKD
Calcium	Every 6–12 mo	Every 3–6 mo	Every 1–3 mo
Phosphorus	Every 6–12 mo	Every 3–6 mo	Every 1–3 mo
PTH	Baseline[b]	Every 6–12 mo	Every 3–6 mo
Alkaline phosphatase	Baseline	Every 12 mo[c,d]	Every 12 mo[c,d]
25-hydroxyvitamin D	Baseline	Baseline	Baseline

[a]More frequent monitoring may be needed in patients receiving treatment.

[b]Subsequent frequency based on baseline concentration and CKD progression.

[c]May be monitored more often in the presence of elevated PTH.

[d]Repeat testing may be determined by baseline value and treatments.

G5D = G5 on dialysis; PTH = parathyroid hormone.

c. Diagnostic testing
    i. Bone mineral density testing: Suggested for patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis if results will affect treatment decisions (KDIGO 2017, grade 2B)
    ii. Bone biopsy: Reasonable if knowledge of type of renal osteodystrophy will affect treatment decisions (KDIGO 2017, not graded)

4. Treatment should be based on serial assessments of phosphate, calcium, and PTH concentrations, considered together (KDIGO 2017, not graded).
    a. Therapy goals for patients with CKD G3a–G5D
        i. Suggest lowering phosphate concentrations toward normal range (KDIGO 2017, grade 2C)
        ii. In adults, suggest avoiding hypercalcemia (KDIGO 2017, grade 2C)
        iii. In patients with CKD G3a–G5 not on dialysis, evaluate for modifiable causes in patients with PTH progressively rising or persistently above the upper normal limit (KDIGO 2017, grade 2C).
        iv. In patients with CKD G5D, suggest maintaining PTH concentrations 2–9 times the upper normal limits. Marked changes in either direction should prompt initiation of or change in therapy (KDIGO 2017, grade 2C).
    b. Nondrug therapy
        i. Dietary phosphorus restriction 800–1000 mg/day in CKD category G3 or higher, alone or in combination with other treatments (KDIGO 2017, grade 2D). Reasonable to consider phosphate source in making dietary recommendations (KDIGO 2017, not graded)
        ii. Dialysis removes various amounts of phosphorus, depending on treatment modalities; however, by itself, dialysis is insufficient to maintain phosphorus balances in most patients.
        iii. Parathyroidectomy: Reserved for patients with unresponsive hyperparathyroidism

c. Phosphate binders: Take with each meal to bind phosphorous in the gut; products from different groups may be used together for additive effect (Table 13).

Table 13. Phosphate Binders[a]

Product	Dosage Form	Typical Mealtime Dose
Calcium carbonate	500, 1000, 1250 mg (40% elemental calcium)	1250 mg
Calcium acetate (PhosLo, Phoslyra)	667-mg capsule, tablet 667 mg/5 mL solution (25% elemental calcium)	2001 mg
Sevelamer hydrochloride (Renagel)	400-, 800-mg tablet	800–2400 mg
Sevelamer carbonate (Renvela)	800-mg tablet 0.8-g, 2.4-g packet	800–2400 mg
Lanthanum carbonate (Fosrenol)	500-, 750-, 1000-mg chewable tablet	250–500 mg
Aluminum hydroxide	320 mg/5 mL suspension	300–600 mg
Ferric citrate (Auryxia)	1 g (210 mg of ferric ion) tablet	2 g (420 mg of ferric ion)

[a]Typical dose is administered three times daily with meals.

i. Decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (KDIGO 2017, not graded).
ii. Calcium-containing binders are often the initial phosphate binder for stage 3 and 4 CKD. Either calcium-containing or nonionic binders can be the initial binder of choice in stage 5 CKD. No data analyses suggest that any phosphate binder is superior to another in clinical outcomes (mortality or hospitalization). In adult patients, suggest restricting the dose of calcium-based phosphate binders (KDIGO 2017, grade 2B)
iii. Aluminum-containing phosphate binders (aluminum hydroxide, aluminum carbonate, and sucralfate) effectively lower phosphorus concentrations. In general, avoid long-term use (grade 1C). Not used as often because of aluminum toxicity (adynamic bone disease, encephalopathy, and erythropoietin resistance). Caution in patients with AKI due to the potential for aluminum toxicity. Use should be limited to a single short-term (4 week) course.
iv. Calcium-containing phosphate binders (calcium carbonate and calcium acetate)
    (a) Widely used phosphate binder. Carbonate salt is inexpensive.
    (b) Carbonate is also used to treat hypocalcemia, which sometimes occurs in patients with CKD, and can decrease metabolic acidosis.
    (c) Calcium acetate is a better binder than carbonate and contains less elemental calcium. Less calcium absorption
    (d) Use may be limited by development of hypercalcemia; consider reducing dose or discontinuing even in the absence of hypercalcemia because of increased harm.
    (e) Total elemental calcium is 2000 mg/day (1500-mg binder; 500-mg diet).
v. Sevelamer: A nonabsorbable phosphate binder
    (a) Effectively binds dietary phosphorus
    (b) As with calcium, considered primary therapy in stage 5 CKD. In particular, consider whether the patient has hypercalcemia or whether calcium intake exceeds the recommended dose with calcium-containing binders.

(c) Decreases low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol.
(d) Metabolic acidosis may worsen with sevelamer hydrochloride, sevelamer carbonate preferred.

vi. Lanthanum carbonate
(a) As effective as aluminum in phosphate-binding capability. Not widely used, but indications similar to sevelamer
(b) Flavorless, chewable tablet
(c) Consider using if patient has hypercalcemia

vii. Ferric citrate: Iron-based phosphate binder
(a) 1 g of ferric citrate contains 210 mg of ferric ion.
(b) Initial dose: 2 tablets (420 mg ferric ion) three times daily with meals
(c) GI adverse effects and potential drug interactions similar to other oral iron preparations

viii. Sucroferric oxyhydroxide: Iron-based phosphate binder
(a) Initial dose: 500 mg three times daily with meals
(b) Tablet must be chewed.
(c) GI adverse effects and potential drug interactions similar to other oral iron preparations

d. Vitamin D and vitamin D analogs: Suppress PTH synthesis and reduce PTH concentrations; therapy is limited by resultant hypercalcemia

i. In adults with CKD G3a–G5, routine use of calcitriol and vitamin D analogs is not suggested (KDIGO 2017, grade 2C). Reasonable to reserve for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (not graded)

ii. Ergocalciferol (vitamin D_2): Inactive form of vitamin D. May be used in stage 3 or 4 CKD for patients with low serum 25-hydroxyvitamin D concentrations; repeat vitamin D concentrations after 6 months of therapy. Usually doses weekly or monthly (Table 14)

iii. Cholecalciferol (vitamin D_3): Inactive vitamin D. May be used as alternative to ergocalciferol. Usually dosed daily

iv. Calcifediol (25-hydroxyvitamin D_3): Undergoes 1-α-hydroxylation to calcitriol. May be used in patients with stage 3 or 4 CKD as alternative to ergocalciferol

Table 14. Ergocalciferol Repletion

Serum 25-Hydroxyvitamin D (ng/mL)	Assessment	Dosing Regimen
< 5	Severe deficiency	Weekly oral doses × 12 wk, then monthly *or* Single intramuscular dose
5–15	Mild deficiency	Weekly oral doses × 4 wk, then monthly
16–30	Insufficiency	Monthly oral doses

v. Calcitriol (Calcijex, Rocaltrol): The pharmacologically active form of 1,25-dihydroxyvitamin D_3 is FDA label approved for managing hypocalcemia and preventing and treating secondary hyperparathyroidism.
(1) Oral and parenteral formulations
(2) Does not require hepatic or renal activation
(3) Low-dose daily oral therapy reduces hypocalcemia but does not significantly reduce PTH concentrations.
(4) High incidence of hypercalcemia, limiting PTH suppression
(5) Dose adjustment at 4-week intervals

vi. Paricalcitol (Zemplar): Vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
  (1) Parenteral and oral formulations
  (2) Does not require hepatic or renal activation
  (3) Lower incidence of hypercalcemia than with calcitriol (decreased mobilization of calcium from the bone and decreased absorption of calcium from the gut)

vii. Doxercalciferol (Hectorol): Vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
  (1) Parenteral and oral formulations
  (2) Prodrug; requires hepatic activation; may have more physiologic concentrations
  (3) Lower incidence of hypercalcemia than with calcitriol (decreased mobilization of calcium from the bone and decreased absorption of calcium from the gut)

e. Calcimimetics: Indicated for secondary hyperparathyroidism, especially in patients with high calcium and phosphate concentrations when vitamin D analogs cannot be used or cannot be increased

i. Cinacalcet hydrochloride (Sensipar): A calcimimetic that attaches to the calcium receptor on the parathyroid gland and increases the sensitivity of receptors to serum calcium concentrations, thus reducing PTH
  (1) Initial dose is 30 mg by mouth once daily, irrespective of PTH concentration.
  (2) Monitor serum calcium within 1 week after starting therapy or increasing the dose (risk of hypocalcemia is about 5%); do not initiate therapy if corrected serum calcium is less than 8.4 mg/dL.
  (3) Monitor PTH (at least 12 hours post-dose) 1–4 weeks after initiating or adjusting therapy.
  (4) Can be used in patients irrespective of phosphate binder or vitamin D analog use
  (5) Caution in patients with seizure disorder (hypocalcemia may exacerbate)
  (6) Adverse effects are nausea (30%) and diarrhea (20%).
  (7) Cinacalcet inhibits cytochrome P450 (CYP) 2D6 metabolism, thereby inhibiting the metabolism of CYP2D6 substrates such that dose reductions in drugs with narrow therapeutic indices may be required (e.g., flecainide, tricyclic antidepressants, thioridazine).
  (8) Cinacalcet is metabolized primarily by CYP3A, so drugs that are potent inhibitors of CYP3A (ketoconazole) may increase cinacalcet concentrations by up to 2-fold.

ii. Etelcalcetide (Parsabiv): A synthetic peptide calcimimetic that activates the calcium-sensing receptor on the parathyroid gland, thus reducing PTH
  (1) Initial dose is 5 mg intravenously three times per week after HD.
  (2) Dose can be titrated in 2.5- to 5-mg increments at intervals of at least every 4 weeks.
  (3) If doses are missed for more than 2 weeks, reinitiate therapy at 5 mg three times per week.
  (4) Monitor corrected serum calcium before initiation and 1 week after initiation or dose adjustment. Once the dose is stabilized, monitor serum calcium every 4 weeks.
  (5) Monitor serum PTH before initiation and 4 weeks after initiation or dose adjustment.
  (6) Adverse effects include hypocalcemia, nausea, diarrhea, QT prolongation; may worsen heart failure
  (7) Use with caution in patients with seizure disorder (hypocalcemia may exacerbate).
  (8) Discontinue cinacalcet for at least 7 days before initiating etelcacetide, and discontinue etelcalcetide for 4 weeks before initiating cinacalcet..

f. Osteoporosis treatment

i. CKD category G1–G2 with osteoporosis and/or high risk of fracture, manage as for the general population (KDIGO 2017, grade 1A)

ii. CKD category G3a–G3b with normal PTH and osteoporosis and/or high risk of fracture, suggest treatment as for the general population (KDIGO 2017, grade 2B)

iii. CKD category G3a–G5D with biochemical abnormalities of CKD-MBD and low bone mineral density and/or fragility fractures, treatment choices consider the magnitude and reversibility of biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (KDIGO 2017, grade 2D)

Patient Case

18. A 40-year-old patient on dialysis with a history of grand mal seizures takes phenytoin 300 mg/day. His albumin concentration is 3.0 g/dL. His total phenytoin concentration is 5.0 mcg/mL. Which best interprets the phenytoin concentrations?
    A. Subtherapeutic; a dose increase is needed.
    B. Therapeutic; no dosage adjustment is needed.
    C. Toxic; a dose reduction is needed.
    D. Not interpretable.

VI. DOSAGE ADJUSTMENTS IN KIDNEY DISEASE

A. The dosages of many drugs will require adjustment to prevent toxicity in patients with CKD. Adjustment strategies vary depending on whether the patient is receiving RRT and, if so, which type. The National Kidney Disease Education Program of the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases suggests that either eGFR or eCrCl be used for drug dosing. If eGFR is used in very large or small patients, it should be multiplied by the actual body surface area to obtain eGFR in milliliters per minute.

B. Pharmacokinetic Principles Guiding Therapy Adjustments
    1. Absorption: Oral absorption can be decreased.
        a. Nausea and vomiting
        b. Increased gastric pH (uremia)
        c. Edema
        d. Physical binding of drugs to phosphate binders
    2. Distribution
        a. Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes.
        b. Acidic and neutral protein-bound drugs are displaced by toxin buildup. Other mechanisms include conformational changes of the plasma protein–binding site. Phenytoin is a classic example. The "normal" free fraction of phenytoin is 10%. Free fraction can be as high as 30% in patients with ESRD and hypoalbuminemia. Metabolic acidosis also increases dissociation of phenytoin from protein-binding sites.
            i. Hypoalbuminemia correction:

$$\text{concentration adjusted} = \text{concentration measured}/[(0.2 \times \text{measured albumin}) + 0.1]$$

            ii. Renal failure adjustment:

$$\text{concentration adjusted} = \text{concentration measured}/[(0.1 \times \text{measured albumin}) + 0.1]$$

            iii. Patients have lower total concentrations despite having adequate free concentrations (increased free fraction).
            iv. Empiric dosage adjustments are usually not needed for phenytoin in patients with kidney disease. However, interpretation of serum phenytoin concentrations should consider alterations in plasma protein binding.

3. Metabolism: Variable changes can occur with uremia; metabolites can accumulate.
4. Excretion: Decreased

C. Pharmacodynamic changes can also occur (e.g., patients with CKD can be more sensitive to benzodiazepines).

D. General Recommendations
   1. Patient history and clinical data
   2. Estimate CrCl (Jelliffe or Brater equation in AKI; Cockcroft-Gault or MDRD study equations in stable kidney function).
   3. Identify medications that require modification (Table 15).

Table 15. Dose Adjustments and Precautions in Decreased Kidney Function

Drug Class	Agents Requiring Dose Adjustment
Antibiotics	Almost all antibiotics require dosage adjustment (exceptions: ceftriaxone, clindamycin, linezolid, metronidazole, macrolides, nafcillin[a])
Anticoagulants	Enoxaparin, fondaparinux, apixaban, rivaroxaban, edoxaban, dabigatran
Cardiac medications	Atenolol, ACEIs, digoxin, nadolol, sotalol; avoid potassium-sparing diuretics if CrCl < 30 mL/min/1.73 m^2
Lipid-lowering therapy	Clofibrate, fenofibrate, statins (particularly rosuvastatin)
Narcotics	Codeine, use caution with meperidine and morphine; other agents may also accumulate
Antipsychotic and antiepileptic agents	Chloral hydrate, gabapentin, lacosamide, levetiracetam, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin
Hypoglycemic agents	Acarbose, alogliptin, canagliflozin, chlorpropamide, dapagliflozin, exenatide, glyburide, glipizide, insulins, liraglutide, metformin, saxagliptin, sitagliptin
Antiretrovirals	Individualize therapy: Monitor $CD4^+$ counts, viral load, and adverse effects (agents requiring dose adjustment: lamivudine, adefovir, emtricitabine, didanosine, stavudine, tenofovir, and zidovudine)

[a]Nafcillin requires dosage adjustment with concomitant renal and liver failure

4. Calculate drug doses individualized for the patient.
   a. Published data
   b. Rowland-Tozer estimate
      i. $Q = 1 - [Fe(1 - KF)]$
      ii. Q = kinetic parameter or drug dose adjustment factor
      iii. Fe = fraction of drug excreted unchanged in the urine
      iv. KF = ratio of patient's CrCl to normal (120 mL/minute/1.73 m^2)
5. Monitor patient (e.g., kidney function, clinical parameters) and drug concentration (if applicable).
6. Revise regimen as appropriate.

E. Drug Dosing in HD
   1. Dosing changes in patients with HD may be necessary because of accumulation caused by kidney failure *or* because the procedure may remove the drug from the circulation *or* because of pharmacodynamic effects (e.g., blood pressure medication reduction because of intradialytic hypotension).
   2. Drug-related factors affecting drug removal during dialysis
      a. Molecular weight: With high-flux membranes, larger molecules (e.g., vancomycin) can be removed compared with conventional filters.
      b. Water soluble: Insoluble drugs are not likely to be removed.

   c. Protein binding: Because albumin cannot pass through membranes, protein-bound drugs cannot pass through either.
   d. Volume of distribution: Drugs with a small volume of distribution (less than 1 L/kg) available in central circulation for removal. Large volumes of distribution cannot be removed (digoxin and tricyclic antidepressants), even if the protein binding is very low.
3. Procedure-related factors affecting drug removal
   a. Type of dialyzer: High flux, widely used now
   b. Blood flow rate: Elevated rates increase delivery and maintain gradient across membrane.
   c. Duration of dialysis session
   d. Dialysate flow rate. High rates of flow increase removal by maintaining the gradient across membranes.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient has AKI on the basis of either the increase in SCr of greater than 0.3 mg/dL in the past 24 hours or the decrease in urinary output of less than 0.5 mL/kg/hour (Answer D is incorrect). The patient's SCr concentration has increased by more than 1.9 times baseline, so it is not stage 1 (Answer A is incorrect). The SCr concentration has not increased more than 3 times baseline or achieved a concentration of greater than 4 mg/dL, and the patient has not required RRT, so it should not be classified as stage 3 (Answer C is incorrect). His urinary output of greater than 0.3 mL/kg/hour is also not consistent with stage 3 AKI. The increase in SCr of 2.0–2.9 times baseline and the patient's urinary output of less than 0.5 mL/kg/hour for more than 12 hours are both consistent with stage 2 AKI (Answer B is correct).

2. Answer: D

Fractional excretion of sodium can help distinguish prerenal AKI from intrinsic AKI. This calculation requires both urinary and serum concentrations of sodium and creatinine from a spot urine sample: FENa = [(urinary sodium/serum sodium)/(urinary Cr/SCr)] × 100 = [(45/140)/(20/2.1)] × 100 = 3.4% (Answer D is correct; Answers A–C are incorrect). This is greater than 2% and is consistent with decreased sodium reabsorption and increased renal sodium excretion.

3. Answer: B

This patient has AKI, probably because of ATN, a type of intrinsic renal failure (Answer B is correct). Hypotension despite rapid fluid resuscitation can cause ATN. The rapid rise in SCr, the BUN/SCr ratio of about 10:1, and the presence of muddy casts on urinalysis all suggest ATN. The FENa greater than 2% is also consistent with intrinsic AKI. There is no evidence of prerenal causes (volume depletion). The absence of an elevated BUN/SCr ratio greater than 20:1 and absence of low urinary sodium and low FENa are all suggest it is not prerenal AKI (Answer A is incorrect). Although lisinopril can cause a functional AKI, this usually occurs with initiation of therapy and presents similarly to prerenal AKI (Answer D is incorrect). Answer C is incorrect because there is no evidence of obstruction in this patient with urinary output present through the urinary catheter.

4. Answer: A

One strategy in managing AKI is to remove potentially nephrotoxic drugs, either direct toxins or medications that alter intrarenal hemodynamics. The following orders are common for patients in AKI: no ACEIs, ARBs, NSAIDs, or intravenous contrast. However, low-dose aspirin can be continued without adversely affecting kidney function (Answer D is incorrect). It is also important to remove (or reduce the dose of) agents that are cleared renally. Metformin, which accumulates in decreased kidney function, should temporarily be discontinued at this time because of an increased risk of lactic acidosis, not because of an adverse effect on kidney function (Answer B is incorrect). In this case, lisinopril is most likely to affect kidney function, so it should be discontinued (Answer A is correct). Unlike NSAIDs, acetaminophen does not interfere with prostaglandin synthesis peripherally; thus, it does not cause hemodynamically mediated AKI (Answer C is incorrect).

5. Answer: C

This patient presents with ATN, anuria, and volume overload. Although loop diuretics have not been shown to improve clinical outcomes in patients with AKI, they may increase urinary output, which will help with fluid and electrolyte balance. In addition, this patient is hypervolemic, so a trial of intravenous loop diuretics would be appropriate (Answer C is correct). Adding 0.9% sodium chloride (Answer A) would worsen fluid overload. Hydrochlorothiazide (Answer B) would not be appropriate because thiazide diuretics are unlikely to be effective with such poor kidney function. Fluid restriction (Answer D) may be necessary if furosemide fails to increase urinary output, but it would not be the first-line approach.

6. Answer: A

Intravenous 0.9% sodium chloride is considered the most effective hydration for preventing contrast-induced nephropathy (Answer A is correct). The other solutions, particularly oral, would not be appropriate because they are less effective at extracellular volume expansion (Answers B, C, and D are incorrect). Although not listed as a choice, intravenous sodium bicarbonate solutions have also been evaluated in this setting and offer no advantage over normal saline.

7. Answer: B

Contrast-associated nephropathy is associated with an acute rise in BUN and SCr within 24–48 hours, with a peak at 3–5 days. Monitoring of SCr at 24 hours (Answer B is correct) will help identify the development of contrast-associated nephropathy. In contrast, 6 hours is too early to detect a significant change (Answer A is incorrect), and waiting more than 48 hours would delay the detection of renal damage (Answers C and D are incorrect).

8. Answer: B

The patient's CKD should be classified as KDIGO category 3a (GFR 45–59 mL/minute/1.73 m^2) (Answer B is correct), which can be calculated by the MDRD formula or Cockcroft-Gault. The five categories range from mild kidney damage (G1) to kidney failure (G5). A patient's CKD would be classified as category G2 if the GFR were 60–89 mL/minute/1.73 m^2 (Answer A is incorrect), category G3b if the GFR were 30–44 mL/minute/1.73 m^2 (Answer C is incorrect), or category G4 if the GFR were 15–29 mL/minute/1.73 m^2 (Answer D is incorrect).

9. Answer: C

The KDIGO guideline also provides guidance on categorizing albuminuria according to the urinary ACR. This patient has category A3, or severely increased albuminuria, given the patient's ACR greater than 300 mg/g (Answer C is correct). Category A2 is moderately increased albuminuria with an ACR of 30–300 mg/g (Answer B is incorrect). Category A1 is an ACR less than 30 mg/g (Answer A is incorrect). Nephrotic-range proteinuria requires protein excretion exceeding 3 g/day (Answer D is incorrect).

10. Answer: C

Given the diagnosis of diabetes mellitus and the presence of severe albuminuria, this patient probably has diabetic nephropathy. Progression will be accelerated by smoking, poor diabetes control, and poor blood pressure control. In patients with diabetes, a target A1C of less than 7% is associated with a decrease in the rate of disease progression. Blood pressure control of less than 130/80 mm Hg in patients also decreases the progression of kidney disease. The standard of care in patients with diabetic nephropathy is ACEIs (evidence for reduced mortality and reduced progression of CKD) or ARBs (evidence for reduced progression but no mortality data), so enalapril (Answer C) is the best choice. A nondihydropyridine (Answer B) might be initiated in patients who cannot tolerate ACEI or ARB therapy, but this would not be a choice yet. Dihydropyridine therapy (Answer A) is not recommended in diabetic nephropathy because of conflicting literature on its efficacy. An increase in atenolol (Answer D) might control blood pressure, but inhibition of the renin-angiotensin system is still the best answer. In addition, a meta-analysis evaluating atenolol in patients with hypertension and diabetes mellitus found either no difference or worse outcomes.

11. Answer: A

The patient's blood pressure is not controlled to KDIGO goal of SBP less than 120 mm Hg. To improve blood pressure control and increase the effect of the ACEI, chlorthalidone should be added (Answer A). Monitoring of SCr and serum potassium is appropriate in this patient. The SCr increase is less than 30%, so enalapril should be continued, making Answers B and C incorrect. Adding chlorthalidone will also counter the tendency for hyperkalemia. Answer D would likely lower blood pressure but would not be the preferred approach because renal protection would probably not be improved.

12. Answer: B

Calculation of the number needed to harm (NNH) is similar to calculation of the number needed to treat but is focused on a negative outcome. In this study, the risk of AKI was 11% in the monotherapy group and 18% in the combination therapy group, a difference of 7%. The NNH is calculated as 1/(absolute risk increase) = 1/(0.07) = 14.3. Hence, the best estimate is that one additional patient would develop AKI for about every 14 patients treated with combination therapy compared with ARB therapy alone (Answer B is correct; Answers A, C, and D are incorrect). When calculating the NNH, it is best to round the number down to the nearest whole number, in contrast to calculating the number needed to treat, when the number is rounded up.

13. Answer: D

A native arteriovenous fistula (Answer D) is the preferred access for chronic HD. If an arteriovenous fistula cannot be constructed, a synthetic arteriovenous graft (Answer C) is considered second line. A subclavian catheter (Answer A) would be a poor choice because of the greater risk of infection and thrombosis and because of the poor blood flow obtained through a catheter. A

Tenckhoff catheter (Answer B) is incorrect because this is a catheter for peritoneal dialysis.

14. Answer: D

The best-studied agent is midodrine, an α_1-agonist (Answer D). Levocarnitine (Answer A) has been tried, but data are limited on its benefit. Fludrocortisone (Answer C) is a synthetic mineralocorticoid that is used for hypotension in other situations; however, its primary mechanism is caused by sodium and water retention in the kidney; therefore, this drug is less likely to work. Sodium chloride tablets (Answer B) would not work acutely, and they should generally be avoided.

15. Answer: C

Empiric coverage for the treatment of peritoneal dialysis–related peritonitis should include activity against both gram-positive and gram-negative organisms (Answers B and D are incorrect). Intraperitoneal administration is preferred to intravenous administration. Cefazolin will provide activity against *Staphylococcus* unless an area has a high rate of methicillin-resistant organisms (Answer C). The choice of antibiotic for gram-negative coverage can include a third-generation cephalosporin with activity against *Pseudomonas* (e.g., ceftazidime, cefepime) (Answer C) or an aminoglycoside. Short-term use of an aminoglycoside should not adversely affect residual renal function. For patients with dialysis-related peritonitis, empiric anaerobic coverage is unnecessary (Answers A and B are incorrect).

16. Answer: A

Hyperparathyroidism is associated with epoetin resistance in patients on HD (Answer A). Although iron deficiency is the most common cause of epoetin deficiency, this patient's laboratory results do not indicate iron deficiency (Answer B) because TSAT is greater than 30% and serum ferritin is greater than 500 ng/mL. Phenytoin therapy (Answer C) has been associated with anemia in other patient populations but not in patients on HD. Infection (Answer D) and inflammation are very common causes of epoetin deficiency in patients on HD, but nothing in this patient's presentation suggests an infectious or inflammatory process.

17. Answer: B

This patient needs treatment for his elevated PTH (800 pg/mL), which places him at high risk of renal osteodystrophy and vascular calcification. He has high serum phosphorus, and although the measured serum calcium concentration is normal, his corrected calcium concentration is elevated, given the presence of hypoalbuminemia (corrected calcium is 10.7 mg/dL). Current phosphate binder therapy is contributing to calcium exposure; therefore, calcium acetate should be discontinued and sevelamer initiated; also, cinacalcet should be added, which will lower PTH and, potentially, serum calcium (Answer B is correct). Answer A is incorrect because increasing the calcium acetate may worsen the hypercalcemia. Answer C is incorrect for two reasons. First, the patient needs some type of phosphate binder; second, intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated PTH in the presence of hyperphosphatemia. Answer D is incorrect because intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated PTH in the presence of hyperphosphatemia. Because this patient also has a seizure disorder, close monitoring of serum calcium concentrations is recommended with the introduction of cinacalcet and discontinuation of calcium acetate. Significant reductions in serum calcium can lower the seizure threshold and potentially worsen seizures.

18. Answer: B

The presence of kidney failure and low serum albumin concentrations results in an increased free fraction of phenytoin, so the measured phenytoin concentration cannot be assumed to be subtherapeutic because it is less than 10 mcg/mL (Answer A is incorrect). However, the concentration can be interpreted with proper adjustment for the presence of renal failure and the patient's measured serum albumin (Answer D is incorrect). Use of the formula that adjusts for hypoalbuminemia in a patient with normal renal function would indicate the concentration is subtherapeutic, but this is not appropriate for a patient on dialysis (Answer A is incorrect). Using the correction equation for a patient with renal failure (adjusted phenytoin concentration = concentration measured/[(0.1 × albumin) + 0.1] = (5.0 mcg/mL)/[(0.1 × 3.0) + 0.1] = (5.0)/(0.4) = 12. 5 mcg/mL) gives a corrected phenytoin concentration within the therapeutic range (Answer B is correct; Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Initial treatment of AKI requires identifying and reversing (if possible) the insult to the kidney. This patient's symptoms and presentation are consistent with prerenal azotemia because of volume depletion, so fluid administration would be the best choice (Answer C is correct). The patient has no suggestion of obstruction (e.g., distended abdomen, history of benign prostatic hypertrophy) (Answer B is incorrect). Diuretic administration would be inappropriate because it would worsen his volume depletion and probably further impair his kidney function (Answer A is incorrect). Fluid management is critical to managing AKI, necessitating a careful patient assessment. Although his glucose concentration is elevated, insulin is not necessary at this time (Answer D is incorrect).

2. Answer: C

The patient has intrinsic AKI (i.e., ATN). Aminoglycosides can cause direct damage to the tubules. In ATN, the BUN/SCr ratio would be normal (10–15:1), whereas an elevated BUN/SCr ratio (greater than 20:1) reflecting hypovolemia is common in prerenal azotemia (Answer A is incorrect). Urinary sodium of less than 20 mEq/L is also a marker of hypovolemia and would be consistent with prerenal azotemia AKI (Answer D is incorrect). Fractional excretion of sodium also distinguishes prerenal and intrinsic renal damage. A low FENa (less than 1%) in an oliguric patient suggests that tubular function is still intact, whereas a FENa greater than 2% is common in intrinsic renal failure (Answer C is correct). Cellular debris is often present in intrinsic renal failure because of renal tubular cell death or damage, whereas a normal urinalysis would be more consistent with prerenal AKI (Answer B is incorrect).

3. Answer: D

While the method of dialysis can affect the extent of drug removal, the pharmacokinetic properties of medications is also important in determining drug removal. Drugs that are highly protein bound (>90%) are not well dialyzed because of the large molecular weight of the binding proteins (Answers A and C are incorrect). Those drugs that are widely distributed (i.e., volume of distribution > 2 L/kg) are also poorly removed by dialysis because such a small amount of drug is in the central compartment (Answers A and B are incorrect). A drug that has a relatively small volume of distribution (0.3 L/kg) and low protein binding (30%) will be most effectively removed by dialysis (Answer D is correct).

4. Answer: A

This patient is likely producing less creatinine, given his cancer, and associated decrease in muscle mass. Because his actual body weight is less than his ideal body weight, it is a better indicator of creatinine production; thus, it should be used in the Cockcroft-Gault formula (Answers C and D are incorrect). Although there is concern about the low SCr concentration in patients with malnutrition, measured SCr for use in the Cockcroft-Gault formula provides a better estimate of renal function than rounding the value to 1 mg/dL (Answers B and D are incorrect). Answer A is correct because it incorporates actual body weight and the measured SCr concentration.

5. Answer: C

This patient's Hgb is not at goal (greater than 10 g/dL), so maintaining the current regimen would not be appropriate (Answer D is incorrect). Iron studies show the patient is iron deficient, with TSAT less than 30% and ferritin less than 500 ng/mL (Answer A is incorrect). Increasing the epoetin dose would not increase red blood cell production in the absence of adequate iron. Although a trial of oral iron might be indicated in non–dialysis patients with CKD, patients on HD should be given intravenous iron as first line (Answer B is incorrect; Answer C is correct).

6. Answer: B

The presence of hypotension despite adequate hydration, a normal BUN/SCr ratio (10–15:1), urinary osmolality, and presence of urinary casts all point to ATN (Answer B is correct). Prerenal AKI is unlikely, considering adequate hydration, high urinary sodium (greater than 40 mEq/L), and lack of high urinary osmolality (Answer A is incorrect). Functional AKI would look similar to prerenal AKI on urinalysis with low urinary sodium and no tubular casts (Answer D is incorrect). Classically, AIN would present with eosinophils in the urine (Answer C is incorrect).

7. Answer: B

Hemoglobin represents continuous data. Because each treatment is administered to a separate group of patients, the data are not paired (i.e., they are unpaired) (Answer A is incorrect). Assuming the data are normally distributed, continuous unpaired data should be evaluated using a t-test (Answer B is correct). Analysis of variance can be used for continuous data, but only when three groups of data are compared (Answer C is incorrect). A chi-square test is used for nominal data (Answer D is incorrect).

8. Answer: D

A cost-utility analysis is an extension of the cost-effectiveness analysis in which the outcomes measured are lives saved, adjusted for changes in quality of life, measured as quality-adjusted life-years (Answer D is correct). A cost-minimization study compares the costs and consequences of two or more interventions that have equivalent outcomes, so the primary focus is on cost (Answer A is incorrect). A cost-effectiveness analysis compares costs and consequences to determine which treatment can achieve the best outcomes at the lowest cost (Answer B is incorrect). A cost-benefit analysis measures costs and consequences in monetary terms; this analysis may be useful to compare costs with unrelated outcomes (Answer C is incorrect).

9. Answer: C

Calculating the FENa helps assess AKI to help differentiate prerenal from ATN: FENa = [(urinary sodium)/(serum sodium)]/[(urinary creatinine)/(SCr)] × 100 = [(24 mEq/L)/(134 mEq/L)]/[(14.3 mg/dL)/(1.8 mg/dL)] × 100 = 2.3% (Answer C is correct). This FENa greater than 2% would be most consistent with ATN (Answers A, B, and D are incorrect).

10. Answer: B

The 2021 KDIGO guidelines recommend that adults with hypertension and CKD be treated to a goal SBP of less than 120 mm Hg (Answer C is correct). Previous KDIGO guidelines have recommended blood pressure goals of 130/80 mm Hg or 140/90 mm Hg based on proteinuria; however, newer guidelines recommend a lower target (Answers A, B, and D are incorrect).

11. Answer: D

This patient whose eGFR is 55 mL/minute/1.73 m^2 would be classified as having stage 3 CKD because his eGFR is less than 60 mL/minute/1.73 m^2. He does not currently have anemia because his Hgb concentration is greater than 13 g/dL. Therefore, Hgb should be monitored according to his CKD stage. For stage 3 CKD, monitoring is recommended at least every 12 months (Answer D is correct). For patients with stage 4 and stage 5 CKD who are not yet receiving dialysis, monitoring should occur at least every 6 months (Answer C is incorrect). Monitoring should occur at least every 3 months once patients in stage 5 CKD are receiving dialysis (Answer B is incorrect). Monthly monitoring is never recommended for a patient who is not currently anemic (Answer A is incorrect).

12. Answer: B

Many factors can contribute to the development of CKD-MBD, including hyperphosphatemia, hypocalcemia, decreased vitamin D and decreased production of active 1,25-dihydroxyvitamin D, and hyperparathyroidism. Although this patient's PTH concentration is elevated, it may be related to hyperphosphatemia. Therefore, the first approach would be to administer a phosphate binder such as sevelamer carbonate to decrease his serum phosphate concentrations (Answer B is correct). Ergocalciferol is not necessary in this patient because the 25-hydroxyvitamin D concentration is greater than 30 ng/mL, indicating adequate intake (Answer A is incorrect). The 2017 KDIGO CKD-MBD guidelines suggest that calcitriol should not be routinely used in G3–G5 CKD, but in G4–G5 CKD for patients with severe and progressive hyperparathyroidism (Answer C is incorrect). Cinacalcet is reserved for patients with hyperparathyroidism despite normalization of phosphate when hypercalcemia is present (Answer D is incorrect).

Geriatrics

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Learning Objectives

1. Evaluate the impact of pharmacokinetic and pharmacodynamic changes in older adults on risk and benefit of medications.
2. Assess inappropriate medication prescribing in older adults using accepted tools.
3. Recommend appropriate pharmacotherapy for patients with dementia, including appropriate interventions for patients with behavioral and psychological symptoms of dementia.
4. Recommend appropriate pharmacotherapy for urinary incontinence and benign prostatic hyperplasia.
5. Evaluate the risks, benefits, safety, and efficacy of medication classes used in the treatment of osteoarthritis, rheumatoid arthritis, and gout.

Abbreviations in This Chapter

AD	Alzheimer disease
ADLs	Activities of daily living
AUASI	American Urological Association Symptom Index
BPH	Benign prostatic hyperplasia
BPSD	Behavioral and psychological symptoms of dementia
CI	Cholinesterase inhibitor
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DMARD	Disease-modifying antirheumatic drug
IADLs	Instrumental activities of daily living
LUTS	Lower urinary tract symptoms
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
OA	Osteoarthritis
PD	Parkinson disease
PSA	Prostate-specific antigen
PVR	Postvoid residual
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SU	Serum urate
TNF	Tumor necrosis factor
UI	Urinary incontinence
ULT	Urate-lowering therapy
XOI	Xanthine oxidase inhibitor

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.

A.B., an 85-year-old man, presents to the primary care clinic 1 month after his spouse's death. His medical history is significant for hypertension, hyperlipidemia, benign prostatic hyperplasia (BPH), and major depressive disorder. His current medications include metoprolol extended release (ER) 25 mg daily, atorvastatin 20 mg daily, tamsulosin 0.4 mg daily, diazepam 5 mg at bedtime as needed for sleep, and escitalopram 10 mg daily. His daughter reports that he has been more lethargic and unsteady during walking over the past 3 days. The patient reports trouble sleeping, necessitating the use of diazepam every night this past week. His blood pressure is 135/72 mm Hg and heart rate is 76 beats/minute. Urinalysis is unremarkable, thyrotropin (TSH) is within the reference range, and Geriatric Depression Scale (GDS) score is 6/15.

1. Which medication is most contributing to A.B.'s lethargy and confusion?
   A. Diazepam.
   B. Metoprolol.
   C. Atorvastatin.
   D. Escitalopram.

2. Which age-related change in pharmacokinetics most likely underlies A.B.'s medication-related problem?
   A. Delayed oral absorption.
   B. Decreased renal excretion.
   C. Slowed metabolism in the liver.
   D. Decreased volume of distribution.

Questions 3 and 4 pertain to the following case.

B.C., a 76-year-old woman, was recently admitted to a long-term care facility for rehabilitation after several falls at home. Her medical history is significant for hypertension, hypothyroidism, Alzheimer disease (AD), hyperlipidemia, and osteoarthritis (OA) of the knee. She takes metoprolol succinate 50 mg daily, levothyroxine 75 mcg daily, atorvastatin 10 mg daily, and donepezil 10 mg daily. Her blood pressure is 126/80 mm Hg and heart rate is 66 beats/minute. Basic

metabolic panel results are all within reference ranges; 25-hydroxyvitamin D concentration is 20 ng/mL, TSH is 1.89 mU/L, TC is 180 mg/dL, LDL is 140 mg/dL, HDL is 35 mg/dL, and TGs are 176 mg/dL. Her Mini-Mental State Examination (MMSE) score is 16/30 and GDS score is 2/15.

3. Which recommendation would be most appropriate to reduce B.C.'s risk of falls?
   A. Initiate memantine 5 mg daily.
   B. Initiate vitamin D 1000 units daily.
   C. Initiate aducanumab 1 mg/kg infusion every 4 weeks.
   D. Initiate calcium carbonate 500 mg twice daily.

4. Which would be most appropriate for B.C.'s OA knee pain?
   A. Ibuprofen 200 mg four times daily.
   B. Acetaminophen 650 mg three times daily.
   C. Tramadol 50 mg three times daily as needed for pain.
   D. Diclofenac 1% topical gel 4 g applied to knee four times daily.

Questions 5–7 pertain to the following case.

C.S., an 80-year-old woman, presents to your clinic accompanied by her daughter, who no longer feels comfortable leaving her mother alone because of her mother's "increasing forgetfulness." The patient's medical history is significant for type 2 diabetes, hypertension, coronary artery disease, congestive heart failure, and OA. She takes the following medications: acetaminophen 650 mg every 6 hours as needed for pain, lisinopril 20 mg daily, furosemide 20 mg daily, potassium chloride 20 mEq daily, carvedilol 12.5 mg twice daily, and glipizide 5 mg daily. Her MMSE score is 18/30. Blood tests obtained last week showed a normal basic metabolic panel, except for a fasting plasma glucose of 65 mg/dL. Her A1C is 5.6%. A urinalysis is unremarkable. No nutritional deficiencies are noted. The patient's blood pressure is 130/80 mm Hg and heart rate is 60 beats/minute. She is diagnosed with AD.

5. Which initial intervention would be most appropriate to help with C.S.'s cognitive function?
   A. Donepezil 10 mg daily.
   B. Galantamine ER 24 mg daily.
   C. Memantine 10 mg twice daily.
   D. Rivastigmine patch 4.6 mg daily.

6. Which intervention would be most appropriate to prevent an adverse drug reaction in C.S.?
   A. Discontinue glipizide.
   B. Discontinue lisinopril.
   C. Reduce carvedilol to 6.25 mg twice daily.
   D. Reduce potassium chloride to 10 mEq daily.

7. One year later, C.S. returns to the clinic. She has moved in with her daughter. Lately, she wanders around the house continuously. She often changes clothes, cries out, and asks repetitive questions. Her current medication regimen includes a rivastigmine 9.5-mg transdermal patch daily, which she has been taking for the past 6 months. Which would be most appropriate for C.S.'s new behavioral symptoms?
   A. Initiate olanzapine 5 mg daily.
   B. Initiate risperidone 0.5 mg twice daily.
   C. Initiate pimavanserin 34 mg daily.
   D. Change acetaminophen to 650 mg every 6 hours around-the-clock.

8. An 80-year-old woman had a total right knee replacement 3 days ago after conservative strategies for OA failed. Her medical history is significant for hypothyroidism, osteoporosis, OA, and hyperlipidemia. Her current medications include simvastatin 20 mg daily, risedronate 35 mg weekly, levothyroxine 75 mcg daily, and oxycodone/acetaminophen 5/325 mg 1 tablet every 4 hours as needed for moderate pain. She is in the hospital preparing for discharge. As the pharmacist counsels the patient on her discharge medication, the patient reports a new onset of "losing her water" the day before and again overnight. Which intervention would be most appropriate for this patient?
   A. Urinalysis.
   B. Pelvic floor exercises.
   C. Mirabegron 25 mg daily.
   D. Duloxetine 20 mg daily.

Questions 9 and 10 pertain to the following case.
P.L., a 69-year-old man, is admitted to the hospital after a motorcycle collision. He had serious injuries resulting in a left leg above-the-knee amputation and has undergone several surgical procedures and rehabilitation in the past 2 weeks. His current medications include tamsulosin 0.4 mg daily, atenolol 25 mg daily, amlodipine 10 mg daily, senna/docusate 8.6/50 mg twice daily, oxycodone controlled release 10 mg every 12 hours, and hydromorphone 4 mg every 3 hours as needed for breakthrough pain (uses 1 or 2 tablets daily). His blood pressure is 155/88 mm Hg, heart rate is 84 beats/minute, and postvoid residual (PVR) volume is 400 mL after voiding 110 mL. His chronic medical conditions are unremarkable except for hypertension, BPH, and gastroesophageal reflux disease.

9. Which intervention would be most appropriate for P.L.?
   A. Change tamsulosin to alfuzosin 10 mg once daily.
   B. Increase atenolol to 50 mg daily.
   C. Change tamsulosin to doxazosin 1 mg daily.
   D. Reduce hydromorphone to 2 mg every 3 hours as needed for breakthrough pain.

10. One year later, P.L. returns for concerns related to BPH. His blood pressure is 118/74 mm Hg, heart rate is 78 beats/minute, and PVR volume is 220 mL after voiding 150 mL. His current medications include doxazosin 4 mg daily, atenolol 25 mg daily, and amlodipine 10 mg daily. Which is the most appropriate intervention for P.L.?
    A. Initiate tadalafil 5 mg daily.
    B. Initiate finasteride 5 mg daily.
    C. Initiate alfuzosin 10 mg daily.
    D. Initiate saw palmetto supplement daily 40 mg injected into affected joint.

11. A 72-year-old woman (height 66 inches, weight 82 kg) whose medical history is significant for rheumatoid arthritis (RA), type 2 diabetes, gastroesophageal reflux disease, and hypothyroidism presents to the clinic with inflammation of the joints of the hands and stiffness lasting 1–2 hours in the morning. She smokes. Her current medications include pantoprazole 40 mg daily, metformin 850 mg twice daily, levothyroxine 100 mcg daily, folic acid 1 mg daily, methotrexate 15 mg weekly, naproxen 500 mg twice daily, calcium 600 mg twice daily, and vitamin D 1000 units twice daily. Her laboratory tests show a positive rheumatoid factor (RF) and positive anti–cyclic citrullinated peptides. The physician determines that this is a flare of severe disease. Which would be the most appropriate intervention for maintenance treatment of this patient's RA?
    A. Change naproxen to prednisone 20 mg daily.
    B. Change methotrexate to 25 mg intramuscularly.
    C. Change methotrexate to leflunomide 20 mg daily.
    D. Administer infliximab 3 mg/kg

12. A 66-year-old man is initiated on allopurinol 100 mg once daily and naproxen 500 mg twice daily for the treatment of an acute gout flare. On diagnosis, no tophi were present, serum urate (SU) was 10.9 mg/dL, and glomerular filtration rate (GFR) was 78 mL/minute/1.73 m^2. His allopurinol dose is increased 2 weeks after initial presentation to 200 mg, and at his 1-month follow-up, the allopurinol dose was further increased to 300 mg once daily. Naproxen was discontinued because his symptoms had resolved; SU was 8.7 mg/dL and GFR was 84 mL/minute/1.73 m^2. He is seen 2 weeks later for an emergency follow-up because he has developed a new rash; SU is 7.4 mg/dL and GFR is 72 mL/minute/1.73 m^2. Which is best for managing his gout at this time?
    A. Increasing allopurinol to 400 mg daily.
    B. Reinitiating naproxen 500 mg twice daily.
    C. Changing allopurinol to febuxostat 40 mg daily.
    D. Changing allopurinol to pegloticase 8 mg intravenously every 2 weeks.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.1 –1.1.3 1.1.6, 1.1.8, 1.1.9,1.1.11, 1.1.13
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.2, 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1, 1.3.2

Systems and Patient-Care Problems:

a. Dementia
b. Behavioral Symptoms of Dementia
c. Urinary Incontinence
d. Benign Prostatic Hyperplasia
e. Osteoarthritis
f. Rheumatoid Arthritis
g. Gout

I. OPTIMIZING PHARMACOTHERAPY IN OLDER ADULTS

A. Aging
   1. Aging is a normal process whereby the human body declines after peak growth and development. In general, aging results as the body responds to environmental stressors according to the person's health and lifestyle factors together with genetic makeup. If environmental stressors are severe enough or individuals have too small a reserve capacity, aging causes frailty, disability, and increased vulnerability to disease and death.
   2. Currently, 54.1 million of Americans (16%) (U.S. Census Bureau 2022) are 65 and older. This is projected to increase to 95 million (23%) by 2060. Older adults constitute about 16% of the population but are responsible for:
      a. 34% of medication costs
      b. 36% of hospital stays
      c. 40% of medication-related hospitalizations
      d. 50% of medication-related deaths
   3. At least $30 billion/year is spent on medication-related morbidity.
   4. There is large heterogeneity in older adults: Racial and ethnic diversity among older adults is increasing, and incomes have a wide range; some people live independently into their 90s and beyond, whereas others become frail and dependent at a younger age. Measurement of aging with years of life is insensitive to the differences between older adults.
      a. If an individual survives to age 65, he or she will likely live an additional 13–20 years.
      b. If an individual survives to age 85, he or she will likely live an additional 6–7 years.

B. Pharmacokinetic Changes Associated with Aging (Table 1)
   1.. Common physiologic changes occur in most older adults, but they are highly variable because of differences in genetics, lifestyle, and environment.

Table 1. Common Physiologic Changes with Age That May Change Drug Pharmacokinetics

Organ System	Physiologic Change with Aging	Effect on Pharmacokinetics
GI	↑ Or no change in stomach pH ↓ GI blood flow Slowed gastric emptying Slowed GI transit	• ↓ Absorption of some drugs and nutrients requiring acidic environment • Absorption rate may be prolonged
Skin	Thinning of dermis Loss of subcutaneous fat	• ↓ Or no change to drug reservoir formation with transdermal formulation
Body composition	↓ Total body water ↓ Lean body mass ↑ Body fat ↓ Or unchanged serum albumin ↑ α1-Acid glycoprotein	• ↑ Volume of distribution and accumulation of lipid-soluble drugs • ↓ Volume of distribution of water-soluble drugs • ↑ Free fraction of highly protein-bound drugs
Liver	↓ Liver mass ↓ Blood flow to the liver ↓ Or no change in CYP enzymes	• ↓ First-pass extraction and metabolism • ↑ Half-life depending on the drug's volume of distribution • ↓ Clearance of drugs with a high first-pass extraction and metabolism • ↓ Or no change in phase I metabolism • No change in phase II drug metabolism

Table 1. Common Physiologic Changes with Age That May Change Drug Pharmacokinetics *(Cont'd)*

Organ System	Physiologic Change with Aging	Effect on Pharmacokinetics
Renal	↓ GFR ↓ Renal blood flow ↓ Tubular secretion ↓ Renal mass	• ↓ Renal elimination of many medications • ↑ Half-life of renally eliminated drugs and metabolites

2. Absorption
    a. Iron, vitamin B_{12}, antifungals, and calcium are decreased with hypochlorhydria or achlorhydria.
    b. Slower gastric emptying may increase the risk of ulceration from aspirin, NSAIDs, bisphosphonates, or potassium chloride tablets.
    c. Most drugs are absorbed by passive diffusion without significant age-related changes.
    d. Transdermal formulations usually require a subcutaneous fat layer to form a drug reservoir for absorption. Use with caution in patients who are thin or who have cachexia.
3. Distribution
    a. Lipid-soluble medications (e.g., diazepam) have an increased half-life in older adults.
    b. Highly albumin-bound drugs (e.g., phenytoin) may have a larger fraction of free (active) drug.
    c. P-glycoprotein, an efflux transporter for several organs including the brain, decreases with aging, which may lead to higher brain concentrations of medications (e.g., opioid analgesics).
4. Metabolism
    a. Morphine and propranolol bioavailability is substantially increased because of a reduction in first-pass metabolism. Expect other drugs with high first-pass metabolism to be similarly affected.
    b. Changes in metabolism through phase I (oxidative) reactions catalyzed by CYP enzymes are variable and confounded by age, sex, concomitant drugs, and genetics.
    c. Lorazepam, oxazepam, and temazepam depend solely on phase II metabolism and are less affected by age-related changes in metabolism.
5. Excretion
    a. Drugs eliminated through glomerular filtration must be dosed according to individual estimated renal function. Chronic medication examples can be found in the 2019 American Geriatrics Society (AGS) Beers Criteria.
    b. The Cockcroft-Gault equation is a validated method for estimating CrCl for drug dosing in older adults. Note the exceptions (e.g., dabigatran, dofetilide, rivaroxaban) that used actual body weight in the Cockcroft-Gault equation during drug development, rather than ideal body weight, which is reflected in the labeled dosing. In addition, clinicians may use adjusted weight for patients with obesity with formulas used for younger adults, though evidence in older adults is lacking.
    c. Some clinicians round the SCr concentration up to 1 mg/dL because older adults have lower muscle mass, which produces less creatinine, and an extremely low SCr would overestimate renal function with these formulas. This rounding is not supported by evidence and remains controversial.

C. Pharmacodynamic Changes Common with Aging
1. Central nervous system: Increased permeability of blood-brain barrier leads to increased sensitivity and adverse effects.
    a. Anticholinergic agents: Confusion, agitation, hallucinations
    b. Benzodiazepines and opioids: Somnolence, confusion, agitation
    c. Antipsychotics and metoclopramide: Extrapyramidal effects and tardive dyskinesia
    d. Tricyclic antidepressants, α-blockers, α_2-agonists: Orthostatic hypotension, drowsiness, confusion

2. Gastrointestinal
    a. Increased pH can lead to decreased vitamin or drug absorption (vitamin B_{12}).
    b. Increased risk of bleeding because of NSAIDs
3. Cardiovascular (CV): Increased catecholamine concentrations lead to down-regulation of β_1-receptors.
    a. Blunted effect of β-blockers
    b. Increased sensitivity to QT-prolonging agents: Antipsychotics, fluoroquinolones, azithromycin
4. Impaired homeostasis
    a. Diuretics, angiotensin-converting enzyme inhibitors: Sodium and electrolytes
    b. Diuretics: Hydration status

Patient Case

Questions 1 and 2 pertain to the following case.

An 85-year-old woman (weight 65 kg) who resides at home with her daughter has a medical history significant for type 2 diabetes and hypertension, and 1 year ago, she had a right hip fracture after a fall. Her regularly scheduled medications include glyburide 10 mg daily, lisinopril 10 mg daily, metformin 500 mg twice daily, aspirin 81 mg daily, and a multivitamin daily. Her as-needed medications include melatonin 6 mg at bedtime as needed for sleep, meclizine 25 mg ½ tablet three times daily as needed for dizziness, and docusate 100 mg twice daily. Her laboratory results show fasting plasma glucose 90 mg/dL, Na 138 mEq/L, K 4.5 mEq/L, Cl 102 mEq/L, CO_2 25 mEq/L, BUN 30 mg/dL, SCr 1.8 mg/dL, and TSH 4.0 mU/L.

1. Considering the potential for altered pharmacokinetics, which pair of medications is most likely to cause problems for the patient?
    A. Aspirin and melatonin.
    B. Lisinopril and meclizine.
    C. Lisinopril and metformin.
    D. Glyburide and metformin.

2. Considering the potential for increased pharmacodynamic sensitivity, which pair of medications is most likely to cause problems for the patient?
    A. Aspirin and melatonin.
    B. Lisinopril and meclizine.
    C. Lisinopril and metformin.
    D. Glyburide and metformin.

D. Drug-Related Risk Assessment for Older Adults
1. Medication overuse
    a. Unnecessary drugs: Use of more medications than clinically indicated and unneeded therapeutic duplication
    b. Common unnecessary drugs: GI agents, CNS agents, vitamins, minerals
    c. Etiology
        i. Prescribing cascade: When a drug is prescribed for treating another drug's adverse effects
        ii. Several prescribers
        iii. Inadequate transitions of care

2. Medication underuse
    a. Omitted but necessary or indicated drug therapy or inadequate dosing
    b. Commonly underused drugs: Anticoagulants, statins, antihypertensives
    c. Medications considered appropriate according to guidelines may be omitted because the prescriber or patient is overly wary of adverse drug effects.
3. Nonadherence
    a. Unintentional nonadherence caused by complex drug regimen
    b. Dementia or other cognitive impairment increases risk.
    c. Cost of medications
    d. Intentional nonadherence because of patient health beliefs or concerns
4. Withdrawal syndromes
    a. Abrupt discontinuation of medication may cause rebound symptoms or delirium.
    b. Common culprits: Antihypertensives, antidepressants, anxiolytics, pain medications
5. Inappropriate medications
    a. Explicit tools: Objective statements that do not require clinical judgment for interpretation
        i. AGS Beers Criteria for potentially inappropriate medication use in older adults
            (a) Evidence-based list of drugs likely to disproportionately affect older adults (i.e., increased risk of falls, confusion, and death)
            (b) Adopted by many federal agencies and Part D plans
            (c) Arranged as drugs and drug classes to avoid, drugs to avoid in certain diseases or conditions, and drugs to be used with caution
            (d) Examples: Anticholinergics, benzodiazepines, sedative-hypnotics, older antipsychotics, select opioids, hypoglycemics, NSAIDs, and proton pump inhibitors
        ii. Another tool popular in European countries is the screening tool of an older person's prescriptions and the screening tool to alert to right treatment (STOPP/START) criteria.
    b. Implicit tools: Patient centered; interpretation requires clinical judgment and patient-specific information. Regarding the Medication Appropriateness Index:
        i. 10 questions to ask about each medication regarding indication, effect, dosing, directions, interactions, duration, and cost
        ii. Indication, effectiveness, and correct dosage carry the most weight.
        iii. Does not assess drug allergies, adverse drug reactions, or adherence
6. Choosing Wisely criteria
    a. 10 things to question in older adults
    b. 7 of the 10 items are drug related.
        i. Antipsychotics in patients with dementia should be avoided.
        ii. The target A1C in diabetes management is 7.5% or higher.
        iii. Avoid benzodiazepines and sedative-hypnotics for insomnia, agitation, or delirium.
        iv. Do not initiate antimicrobials for bacteriuria without symptoms.
        v. Assess the benefit-risk of cholinesterase inhibitors (CIs).
        vi. Appetite stimulants are not helpful for anorexia or cachexia.
        vii. Drug regimen review is necessary with every new prescription.

Patient Case

Questions 3–5 pertain to the following case.

A 70-year-old woman (height 66 inches, weight 71.7 kg [158 lb]) is in the clinic for an evaluation by the clinical pharmacist for polypharmacy. She has concerns of fatigue, light-headedness, constipation, and "too many medicines." Her medical history is significant for hypertension, coronary artery disease (drug-eluting stent 8 years ago), chronic obstructive pulmonary disease, diabetes, incontinence, frequent UTIs, depression, and moderate dementia. Her vital signs include blood pressure 160/82 mm Hg, heart rate 51 beats/minute, respiratory rate 16 breaths/minute, and Sa_{O_2} 99% on room air. Her current medications are as follows: fluticasone/salmeterol 250/50 1 puff twice daily, aspirin 81 mg daily, acetaminophen 650 mg three times daily, clopidogrel 75 mg daily, donepezil 10 mg daily, glipizide 5 mg twice daily, lisinopril 10 mg daily, loratadine 10 mg daily, metoprolol 50 mg twice daily, paroxetine 40 mg daily, ranitidine 150 mg twice daily, simvastatin 40 mg at bedtime, and tolterodine 2 mg at bedtime. Nitrofurantoin 100 mg twice daily for 10 days was initiated 3 days ago. Laboratory values from her physician visit 3 days before are as follows: Na 130 mg/dL, K 4.2 mEq/dL, Cl 99 mg/dL, CO_2 24 mEq/dL, BUN 24 mg/dL, SCr 1.6 mg/dL, fasting glucose 67 mg/dL, A1C 6.3%, urinalysis unremarkable except for blood-small, pH 7.5, RBCs 11–25/high-power field (HPF), white blood cells 0–2/HPF, and bacteria 168/HPF.

3. Which medication list best depicts the medications with the greatest potential to harm this patient, according to the AGS 2019 Beers Criteria?
   A. Paroxetine, donepezil, tolterodine.
   B. Donepezil, glipizide, simvastatin.
   C. Glipizide, donepezil, nitrofurantoin.
   D. Metoprolol, clopidogrel, ranitidine.

4. Given the available patient information, which group of medications is least appropriate for this patient, according to the Medication Appropriateness Index?
   A. Fluticasone/salmeterol, ranitidine, donepezil, tolterodine.
   B. Metoprolol, clopidogrel, ranitidine.
   C. Aspirin, glipizide, donepezil, nitrofurantoin.
   D. Paroxetine, nitrofurantoin, simvastatin.

5. Which medications would best be discontinued, according to the Choosing Wisely criteria?
   A. Paroxetine, ranitidine, donepezil, tolterodine.
   B. Metoprolol, clopidogrel, ranitidine.
   C. Glipizide, donepezil, nitrofurantoin.
   D. Ranitidine, nitrofurantoin, glipizide, tolterodine.

F. Changes in Function Associated with Aging
   1. Quality of life, place of residence, and social and physical function may become more important than duration of life.
   2. Instrumental activities of daily living (IADLs): Examples: Doing housekeeping, using telephone, managing medications, shopping, cooking, managing money
   3. Activities of daily living (ADLs): Examples: Feeding, dressing, bathing, toileting, transferring
   4. Cognitive screening
   5. Mood: Geriatric Depression Scale
      a. More sensitive to older adults
      b. Validated in various settings (e.g., home, long-term care) and in patients with various cognition
      c. The long form is composed of 30 questions; the 15-question tool (GDS-15) is more commonly used. A score of 5 or higher on the GDS-15 suggests depression.
   6. Gait and balance

G. Geriatric Syndromes
   1. Geriatric syndromes follow a concentric model, with many risk factors and several etiologies contributing to a clinical presentation, rather than the linear model with one etiology following a defined pathogenesis.
   2. Falls
      a. Possible etiologies: Psychoactive medications, polypharmacy, orthostatic hypotension, hypoglycemia, hyponatremia, myocardial infarction, UTI
      b. Examples of contributing risk factors: Vitamin D deficiency, poor balance, deconditioning/muscle weakness, poor vision, environment
   3. Delirium
      a. A disturbance in attention and awareness developing over hours to days, with fluctuation
      b. Possible etiologies: Psychoactive medications, polypharmacy, hypoglycemia, hyponatremia, myocardial infarction, infection
      c. Examples of contributing risk factors: Dementia, stroke, vitamin B_{12} deficiency, poor hearing, lack of sleep, constipation, pain, thyroid disorder
   4. Hazards of hospitalization
      a. Immobilization leads to deconditioning, which increases risk of falls and fractures. Regaining what was lost takes longer in older adults.
      b. Immobilization and "tethers" (e.g., intravenous lines, oxygen lines, catheters) necessitate nursing assistance to bathroom. Unavoidable delay may lead to incontinence, catheters, infections, falls, and pressure sores.
      c. Sensory deprivation from isolation and inaccessibility to glasses or hearing aids can lead to delirium.
      d. Prescribed diets or nothing-by-mouth status can lead to an increased risk of dehydration, decreased plasma volume, malnutrition, insertion of feeding tubes, and aspiration pneumonia.
      e. Preventable adverse drug events are common contributors to increased morbidity and mortality in older hospitalized adults.
      f. Early mobility, adequate nutrition, reduced polypharmacy, and early discharge planning may reduce functional disability and length of stay.

Patient Case

Questions 6 and 7 pertain to the following case.

A 70-year-old woman is admitted to the hospital with a broken arm after a fall. While in the hospital, she is on bedrest most of the time, loses 2 kg (current weight 63 kg), and has trouble sleeping. She is to be discharged to a rehabilitation facility for 2–3 weeks of therapy. Her medications at discharge are glipizide 5 mg daily, lisinopril 10 mg daily, aspirin 81 mg daily, a multivitamin daily, mirtazapine 15 mg at bedtime, calcium 500 mg twice daily, and tramadol 25 mg every 8 hours as needed for pain.

1. When recommending medication changes for this patient, which functional assessment is most important to evaluate?
   A. IADLs.
   B. Depression.
   C. Pressure sores.
   D. Gait and balance.

2. To maintain and improve function in this patient, which intervention is best to implement?
   A. Add atorvastatin 10 mg daily.
   B. Increase lisinopril to 20 mg daily.
   C. Add vitamin D 1000 units twice daily.
   D. Change tramadol to naproxen 500 mg twice daily as needed for pain.

II. DEMENTIA

A. Epidemiology
   1. Affects 4–5 million people in the United States
   2. Of people 65 and older, 6% have dementia, increasing to 30%–50% of those 85 and older.

B. Dementia Definition: Cognitive decline in complex attention, executive function, learning and memory, language, and/or perceptual-motor or social cognition AND interferes with work or social functions
   1. Delirium should be ruled out and reversible causes corrected first.
   2. Mild cognitive impairment (MCI) is the condition of people with some deficits in cognition who do not meet the criteria for dementia.
   3. AD is the most common and most studied type of dementia.
   4. Theories of pathogenesis include cholinergic, β-amyloid plaques, tau protein (neurofibrillary tangles), genetics (apolipoprotein E_4), and inflammation (cytokines, prion).

Table 2. Comparisons of Memory Impairment and Dementias with AD

Disease	Differences from AD	Treatment Notes
Common Irreversible Causes		
MCI	No interference with work or social functions One in five patients progress to AD	Eliminate or control risk factors for dementia May use CIs, which reduced risk of progression by 40% in one study
Vascular dementia	Includes focal neurologic signs and symptoms Radiologic evidence of stroke Onset within 3–6 mo of stroke Abrupt deterioration followed by stepwise progression	Control of cardiac and vascular risk factors CIs and memantine not effective
Lewy body dementia	Fluctuating cognition with pronounced variation in attention and alertness Recurrent visual hallucinations Motor features of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use Cis
Dementia of advanced PD	PD onset predates cognitive impairment Usually at latter stages of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use CIs
Frontotemporal dementia	Affects personality, behavior, self-care, and language Onset in ages 45–65 with a 2- to 10-yr course	CIs may worsen behavior and cause agitation SSRIs or trazodone may be beneficial
Reversible Causes		
Vitamin B_{12} deficiency	Progressive memory loss Vitamin B_{12} serum concentration < 300 pg/mL May be anemic also, but folic acid may disguise the anemia	Replace vitamin B_{12} according to standard protocols
Hypothyroidism	Deficient or inadequate replacement of thyroxine	Levothyroxine replacement according to standard protocols
Depression	Trouble with concentration and memory Apathy and "I don't care" responses	Treatment of depression according to standard protocols
NPH	Triad of progressive memory loss, incontinence, and gait abnormality Symptoms improve after lumbar puncture	Surgical placement of ventricular shunt
Medications	Anticholinergics, muscle relaxants, opioids, antiseizure medications, benzodiazepines, and tricyclic antidepressants may increase memory loss and confusion mimicking symptoms of dementia	Decrease dose or deprescribe as appropriate

AD = Alzheimer disease; CI = cholinesterase inhibitor; MCI = mild cognitive impairment; NPH = normal pressure hydrocephalus; PD = Parkinson disease; SSRI = selective serotonin reuptake inhibitor.

C. Assessment Tools
   1. Cognitive assessment tools
      a. Mini-Mental State Examination (Table 3)
         i. 30-point scale; higher score indicates better function
         ii. Untreated AD: Score usually decreases by 3 or 4 points a year.
         iii. Heavily relies on verbal and language skills, so is less accurate if education is poor
         iv. Requires fee to administer examination
      b. SLUMS examination
         i. 30-point scale; higher score indicates better function
         ii. Includes adjustment of scores for lower educational status
      c. Montreal Cognitive Assessment
         i. 30-point scale; higher score indicates better function
         ii. Less reliant on verbal or language skills
         iii. Requires training and fee to use assessment
      d. Mini-Cog assessment
         i. 5-point scale; higher score indicates better function, but does not stage disease
         ii. Easiest to administer; takes 3 minutes
   2. Functional assessment tools: Reisberg Functional Assessment Staging (FAST) scale (Table 4)
      a. 16-item scale correlating with activity limitations and decline associated with AD
      b. Stage 7 associated with prognosis of 6 months or less life expectancy

D. Diagnostic Guidelines
   1. Recognizes three phases:
      a. Preclinical, asymptomatic phase
      b. Symptomatic, predementia phase (MCI)
      c. Dementia phase
   2. Diagnosis may be identified for research purposes by:
      a. Biomarkers of increased tau or decreased β-amyloid concentrations in CSF
      b. Reduced glucose uptake in brain on positron emission tomography scanning using florbetapir F18 or flutemetamol F18
      c. Atrophy of specific brain areas on MRI
   3. Preclinical and predementia phases are targets for investigational studies to halt progression.
   4. For clinicians, diagnosis is typically made without these biomarkers or imaging.

E. Clinical Presentation and Classification

Table 3. Stages of Alzheimer Disease

	MMSE Score (out of 30)	Examples of Cognitive Loss	Examples of Functional Loss
Mild	20–24	Some short-term memory loss; word-finding problems	Loss of IADLs such as laundry, housekeeping, and managing medications; may get lost in familiar places
Moderate	10–19	Disorientation to time and place, inability to engage in activities and conversation	Needs assistance with ADLs such as bathing, dressing, and toileting
Severe	< 10	Loss of speech and ambulation, incontinence of bowel and bladder	Dependency in basic ADLs such as feeding oneself; often needs around-the-clock care

ADLs = activities of daily living; IADLs = instrumental activities of daily living; MMSE = Mini-Mental State Examination.

Table 4. Activity Limitation with AD

FAST Scale Item	Activity Limitation with AD
Stage 1	No difficulty
Stage 2	Subjective work difficulties; forgetting location of objects
Stage 3	Work difficulties evident to coworkers; difficulty traveling to new locations
Stage 4	Difficulty performing complex tasks (finances, planning)
Stage 5	Requires assistance choosing proper clothing (season or occasion)
Stage 6 6a 6b 6c 6d 6e	Decreased ability to independently bathe, dress, and toilet Difficulty dressing properly Unable to bathe properly Unable to toilet properly (forget flushing, improper wiping) Urinary incontinence Fecal incontinence
Stage 7 7a 7b 7c 7d 7e 7f	Loss of speech, ambulation, and consciousness Speech limited to 1–5 words per day Intelligible vocabulary lost Nonambulatory Unable to sit up Unable to smile Unable to hold head up

AD = Alzheimer disease.

F. Management
   1. Goals are to maintain function and cognition.
   2. Nonpharmacologic therapy
      a. Education, especially with caregiver
      b. Physical exercise and mental exercise
      c. Management of comorbid conditions
      d. Avoid alcohol and medications that worsen mentation.

Patient Case

8. An 84-year-old widow lives at home alone. She can perform ADLs and most IADLs with her daughter's assistance. Her current medications are hydrochlorothiazide 12.5 mg daily for hypertension, tolterodine long acting 4 mg daily for incontinence, escitalopram 20 mg daily for depression, acetaminophen 650 mg as needed for arthritis, and calcium/vitamin D for prevention of osteoporosis. The patient's physician administers the MMSE, and her score is 23/30. On physical examination, no cogwheel rigidity or tremor is noted. Which recommendation would be best at this time?

   A. Add donepezil 5 mg daily.

   B. Discontinue tolterodine and reassess the patient.

   C. Add a vitamin B_{12} 1000-mg injection monthly.

   D. Change hydrochlorothiazide to lisinopril 5 mg daily.

3. Pharmacologic therapy (Table 5)
    a. Controversy over significance of clinical response
    b. Mild to moderate AD: Initiate CI.
        i. No evidence that one agent is superior to others
        ii. Titrate to recommended maintenance dose as tolerated.
        iii. May increase to maximum dose if tolerated and maintenance dose no longer effective, or try alternative CI, but clinically meaningful improvement unlikely
    c. Moderate to severe AD: May initiate *N*-methyl-D-aspartate (NMDA) receptor antagonist (memantine), CI, or combination: Slight or no benefit with combination therapy in systematic reviews
    d. Disease-modifying immunotherapies
        i. Antiamyloid monoclonal antibody: Aducanumab
            (a) Accelerated FDA approval for MCI or mild dementia; safety and efficacy in later stages of AD not studied
            (b) Phase III trials showed reduction in amyloid plaques, but modest reduction in cognitive decline
            (c) Infusion every 4 weeks; around $28,200 per year
            (d) In April 2022, the Centers for Medicare & Medicaid determined that aducanumab would only be covered for patients in clinical trials, making its role in therapy still to be determined.
        ii. Anti-tau monoclonal antibody therapies under phase II and phase III clinical trials

Table 5. Comparison of Drugs for AD Treatment

Drug	Starting Dose	Maintenance Dose	Dosage Forms	Adverse Effects	Comments
Cholinesterase Inhibitors					
Donepezil	5 mg daily	10 mg daily May increase to 23 mg/day	Tablets Orally disintegrating tablets	GI: Nausea, vomiting, diarrhea CNS: Headache, insomnia, dizziness Cardiac: Bradycardia, orthostatic hypotension, syncope (AGS Beers Criteria for patients with syncope) Long-term risks: Falls, hip fracture, pacemaker placement	
Rivastigmine	1.5 mg twice daily 4.6-mg patch daily	3–6 mg twice daily 9.5-mg patch daily; may increase to 13.3-mg patch daily	Capsules Oral solution Transdermal patch		Highest rate of GI effects Labeled for dementia with Parkinson disease as well Monitor for skin reactions with patch
Galantamine	4 mg twice daily 8 mg ER once daily	8–12 mg twice daily 8–24 mg ER once daily	Tablets Oral solution ER capsules		Preferable to administer with food Renal dosing adjustment necessary

Table 5. Comparison of Drugs for AD Treatment *(Cont'd)*

Drug	Starting Dose	Maintenance Dose	Dosage Forms	Adverse Effects	Comments
NMDA Receptor Antagonist					
Memantine	5 mg once daily 7 mg ER once daily	10 mg twice daily 28 mg ER once daily	Tablets Oral solution ER capsules	CNS: Headache, dizziness, confusion, agitation, hallucinations GI: Diarrhea, vomiting	Usually well tolerated
Combination Product					
Donepezil/ memantine	10/28 mg once daily in the evening	10/28 mg once daily	ER capsule	See above	Use after stabilized on donepezil and memantine separately Renal dosing adjustment necessary
Disease-Modifying Immunotherapies (anti–amyloid monoclonal antibodies)					
Aducanumab	1 mg/ kg every 4 wk for infusions 1 and 2, then titrate	10 mg/kg every 4 wk for infusions 7–12	IV infusion	Diarrhea, confusion, altered mental status Serious: ARIA-H (micro-hemorrhage), ARIA-E (brain edema, headache), seizure	Only therapy approved for MCI Dose based on actual body weight MRI brain within 1 yr before initiation required; additional MRIs if patient experiences signs/ symptoms of ARIA

AD = Alzheimer disease; ARIA-E = amyloid-related imaging abnormalities-edema; ARIA-H = amyloid-related imaging abnormalities-hemosiderin deposition; IV = intravenous(ly); MCI = mild cognitive impairment.

4. Therapy duration
    a. The Choosing Wisely criteria recommend evaluating with objective tools at 12 weeks and considering discontinuation if the goals of therapy are not met.
    b. Studies investigating long-term efficacy beyond 1 year are limited, but many patients receive the drug for years.
    c. Recommend to discontinue at advanced stages of disease (FAST stage 7)
        i. Tapering is recommended if the patient is taking a high dose.
        ii. Rebound agitation may occur.

Patient Cases

9. An 87-year-old man with AD receives rivastigmine 6 mg twice daily. His family notes improved functional ability but reports that he has nausea and vomiting that appear to be related to rivastigmine. Which recommendation is best for the patient at this time?
   A. Advise the patient to take rivastigmine with an antacid.
   B. Change rivastigmine to the patch that delivers 9.5 mg daily.
   C. Discontinue rivastigmine and initiate memantine 5 mg twice daily.
   D. Add prochlorperazine 25 mg by rectal suppository with each rivastigmine dose.

10. A 75-year-old woman with AD who lives at home with her husband has been treated with donepezil 10 mg daily for about 3 years. When she began therapy, her MMSE score was 21/30; her present MMSE score is 17/30. The patient cannot perform most IADLs but can perform most ADLs with cueing. About 2 months ago, her donepezil dose was increased to 23 mg, but she could not tolerate it, and it was reduced back to 10 mg daily. Her husband asks about changing her drug treatment to help maintain her function. Which is the next best course of action?
   A. Retry donepezil 23 mg daily.
   B. Initiate memantine 5 mg daily.
   C. Initiate an aducanumab 1-mg/kg infusion every 4 weeks.
   D. Change donepezil to a rivastigmine 9.5-mg patch daily.

III. BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

A. Epidemiology
   1. As disease progresses from mild to moderate, behavioral and psychological symptoms of dementia (BPSD) occur. These tend to wane as the disease progresses to severe.
   2. Up to 90% of patients with dementia have BPSD at some point in disease progression.
   3. Associated with high rate of disability, functional decline, poor health outcomes, physical injury, nursing home placement, and emergency services
   4. Behaviors commonly peak during late afternoon or early evening and are thus called “sundowning.”

Table 6. Symptoms During Disease Progression

MMSE Score	Stage	Symptoms
25	Mild	Memory loss Mood swings[a] Apathy Mild executive dysfunction Poor drawing Mild personality changes[a]
20		
15	Moderate	Unable to learn Aggression, psychosis[a] Aphasia, apraxia Confusion, insomnia[a] Wandering, agitation[a] Need for assistance with ADLs
10		
5	Severe	Gait changes[a] Loss of ADLs Incontinence Bed confinement
0		

[a]Noncognitive symptoms.

ADLs = activities of daily living; MMSE = Mini-Mental State Examination.

B. Assessment
   1. Scales are rarely used in nursing homes or clinical practice, but it is important to identify the target behavior, how often it is occurring, and how severe it is in order to assess the treatment response.
   2. Assess for a medical reason that may precipitate the target behavior and treat it, if found.
      a. Pain is a common issue that patients cannot communicate. Treat with scheduled acetaminophen.
      b. Delirium precipitated by medical illness or medication should be ruled out.
      c. Constipation is a common geriatric syndrome and an issue patients cannot communicate. Treat with scheduled bowel regimen.

C. Nonpharmacologic Treatment: Cornerstone of Therapy
   1. The theory is that behavior is the communication of unmet need.
   2. Eliminate antecedents and triggers.
   3. Person-centered interventions: Consider patient's longstanding habits, values, and beliefs; use distraction, music, aromatherapy, and pet therapy.
   4. Symptoms likely to respond: Wandering, hoarding, hiding objects, repetitive questioning, withdrawal, social inappropriateness, apathy

D. Pharmacologic Treatment: None of these are FDA-labeled indications. (Table 7)
   1. Agency for Healthcare Research and Quality has published a summary on the use of atypical antipsychotic agents for off-label indications. Atypical antipsychotics improve behavioral symptoms of dementia, but effect sizes are small and adverse effects are significant.
   2. Retrospective case-control study of older veterans with dementia during a 180-day period indicated haloperidol number needed to harm (NNH) was 8, compared with atypical antipsychotics, with NNH of 14–31 for risk of death.
   3. Antipsychotic medications may increase the risk of death when used in older adult patients with dementia-related psychosis (black box warning).

Table 7. Drug Treatment for BPSD

Symptom	Presentation	Treatment Options After Nonpharmacologic Efforts Ineffective
Anxiety	Part of this is because they cannot remember things	Buspirone or SSRI/SNRI or gabapentin Limit benzodiazepines
Apathy	One of the earliest symptoms Nonpharmacologic treatment tailored to patient's activities	CIs Methylphenidate effective in small, short-term studies
Depression	Up to 80% of patients with AD have depression	SSRI or mirtazapine
Insomnia	Sleep-wake cycle is disrupted	Melatonin Mirtazapine can be considered if concomitant depression
Wandering	Walk so much they begin to lose weight	No drug will stop patients from wandering
Paranoia, hallucinations, sundowning, agitation	They may think that because they cannot find something, you stole it Often accuse spouse of infidelity If psychosis and delusions do not bother anyone, do not use drugs	Risperidone, olanzapine, quetiapine, and aripiprazole have been tried. Use very low doses. ADEs may offset any benefit For patients with parkinsonian symptoms, quetiapine is preferred because of decreased dopaminergic activity and EPS
		Pimavanserin can be used for PD-related psychosis. Use of pimavanserin in AD is being studied
Aggression, resistance to care	Most difficult and best response is to treat nonpharmacologically	Valproic acid products commonly used despite controversial evidence that benefits outweigh risk. Drugs under investigation for agitation include prazosin, dextromethorphan/quinidine, and citalopram

AD = Alzheimer disease; ADE = adverse drug effect; BPSD = behavioral and psychological symptoms of dementia; CI = cholinesterase inhibitor; EPS = extrapyramidal symptoms; PD = Parkinson disease; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Patient Case

Questions 11 and 12 pertain to the following case.

You are evaluating the medication profile of an 87-year-old woman who resides in a secure advanced dementia unit. Her medical history includes dementia (likely AD), Parkinson disease (PD), and OA. She needs assistance with all ADLs, including total assistance with bathing and dressing, as well as help with feeding. She transfers with minimal help to using a wheelchair. Her medication regimen includes donepezil 10 mg daily, memantine 10 mg twice daily, carbidopa/levodopa 25/100 mg four times daily, and a multivitamin supplement daily. The patient's most recent MMSE score is 5/30. When reviewing the nursing notes, you see several references to the patient's continuously crying out, "Help me, help me," beginning around 5 p.m. On medical evaluation, reversible causes of her hypervocalization are ruled out.

11. Which initial approach is most appropriate for this patient?
    A. Initiate ibuprofen 400 mg every 8 hours.
    B. Order haloperidol 1 mg every 6 hours as needed for agitation.
    C. Begin music therapy with songs the patient enjoyed when younger.
    D. Move the patient to a private room to minimize social contacts after 3 p.m.

12. After 2 months, the patient's agitation increases such that the nursing staff cannot bathe or feed her. Assuming nonpharmacologic approaches are ineffective, which is the best pharmacologic approach to treat her behavioral symptoms?
    A. Increase donepezil to 23 mg daily.
    B. Begin melatonin 6 mg at bedtime.
    C. Add quetiapine 25 mg at 4 p.m. daily.
    D. Add citalopram 10 mg daily.

IV. URINARY INCONTINENCE

A. Epidemiology
   1. Prevalence in community-dwelling older adult women is 38%.
   2. Less common in older adult men: 17%
   3. Up to 75% of nursing home residents have urinary incontinence (UI).
   4. Transient incontinence can occur because of DRIP:
      D = Drugs, Delirium
      R = Retention, Restricted Mobility
      I = Impaction, Infection, Inflammation
      P = Polyuria, Prostatitis

B. Physiology
   1. During filling, β_3-adrenergic stimulation relaxes detrusor muscle to increase capacity.
   2. α-Adrenergic stimulation tightens the internal bladder sphincter.
   3. Acetylcholine (M_3 receptors) mediates involuntary and volitional bladder contractions.
   4. Normal bladder emptying occurs with a decrease in urethral resistance and contraction of the bladder muscle.

5. Aging effects include decreased bladder elasticity and capacity, more frequent voiding, decline in bladder outlet and urethral resistance in women with loss of estrogen, and decrease in flow rate in men with prostatic enlargement.

C. Types of UI

Table 8. Common Types of UI and Drug-Induced Causes

Type of Incontinence	Description	Drug-Induced Causes
Urge or overactive bladder	Loss of a moderate amount of urine with an increased need to void Common in patients with AD, PD, MS, and stroke	Cholinergic agents that stimulate the bladder such as bethanechol and CIs
Stress incontinence	Loss of small amounts of urine with increased abdominal pressure (e.g., sneezing, coughing) Stress UI is more common in postmenopausal women	α-Blockers such as prazosin decrease urethral sphincter tone
Overflow incontinence	Loss of urine because of excessive bladder volume caused by outlet obstruction or an acontractile detrusor PVR is often high (> 300 mL), indicating incomplete emptying	Anticholinergic agents, calcium channel blockers, and opioids decrease detrusor muscle contractions
Functional incontinence	Inability to reach the toilet because of mobility constraints	Sedating drugs that cause confusion Diuretics increase voiding
Mixed incontinence	UI that has more than one cause, usually stress and overactive bladder	

AD = Alzheimer disease; CI = cholinesterase inhibitor; MS = multiple sclerosis; PD = Parkinson disease; PVR = postvoid residual; UI = urinary incontinence.

D. Nonpharmacologic Interventions: First-line Therapy
   1. Lifestyle modifications
      a. Weight loss for patients with a BMI greater than 25–30 kg/m^2
      b. Limit/avoid caffeine and alcohol
      c. Quit smoking
      d. Limit fluid intake before bedtime
   2. Stress incontinence
      a. Pelvic floor exercises (Kegel exercises) are first line for stress.
      b. Biofeedback may be needed to teach pelvic floor exercises.
      c. Pessaries (a prosthetic vaginal insertion device) or bulking agent injections also help stress incontinence.
   3. Urge incontinence
      a. Pelvic floor exercises in combination with medication for urge or mixed UI
      b. Bladder training to increase time between voiding in urge incontinence
      c. Peripheral tibial nerve stimulation or sacral neuromodulation techniques are third line after lifestyle and pharmacologic treatments.
   4. Scheduled and timed voiding may be helpful for patients with dementia.
   5. Prostatectomy in men or self-catheterization for severe overflow incontinence

E. Pharmacologic Treatment (Table 9)

Table 9. Recommended Pharmacologic Treatment by Type of Incontinence

Type of Incontinence	Drug Treatment	Comments
Urge or overactive bladder	**Antimuscarinic agents** Oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, darifenacin	Magnitude of clinical efficacy is modest Strong anticholinergic effects (on Beers Criteria) Long-acting formulations preferred because of modest decreased adverse effect profile
	β3-Agonist Mirabegron	Minimal anticholinergic effects Cost is commonly a barrier for patients Can be used in combination with antimuscarinic agents if monotherapy fails Avoid in hypertension
	OnabotulinumtoxinA Intradetrusor or injections	Prevents stimulation of detrusor muscle Must be able to perform self-catheterization
Stress	**α-Adrenergic agonists** Pseudoephedrine, phenylephrine	Efficacy evidence is limited
	Topical estrogens Conjugated estrogen vaginal cream or estradiol vaginal insert or ring	Use if other symptoms of estrogen deficiency Vaginal estrogens may improve severity of stress incontinence
	Serotonin-norepinephrine reuptake inhibitor Duloxetine	Not FDA labeled for stress UI; may reduce the severity of incontinence Adverse effects may limit its usefulness
Overflow	**α-Adrenergic antagonists** Alfuzosin, tamsulosin, silodosin, doxazosin, terazosin, prazosin	Adverse effects vary depending on selectivity to receptors in the bladder or prostate (alfuzosin, silodosin, and tamsulosin are more specific and preferred in older adults)
	5-α-Reductase inhibitors Finasteride, dutasteride	To slow progression Reduce the size of the prostate and alter PSA values
	Cholinomimetics Bethanechol	Stimulates the detrusor muscle but also has systemic cholinomimetic effects
	Phosphodiesterase type 5 inhibitors Tadalafil	5 mg once daily approved for BPH
Functional	No drug treatments	Consider interventions to remove any potential cause, barriers, or obstacles; provide schedules or prompted toileting; assistance may be required to transfer on and off commode
Mixed	Focus on predominating symptoms	Consider treatments for individual components (i.e., stress and urge)

BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen; UI = urinary incontinence.

Patient Case

13. A 75-year-old woman reports urinary urgency, frequency, and loss of urine when she cannot get to the bathroom in time. She also wears a pad at night that she changes two or three times because of incontinence. Her medical history is significant for MCI (MMSE score 25/30), OA, and hypothyroidism. A urinalysis is negative for leukocyte esterase and nitrites. Physical examination is normal, and her PVR is normal (less than 100 mL). Which therapy would be best to initiate for this patient at this time?
    A. Mirabegron.
    B. Darifenacin.
    C. Pelvic floor exercises and solifenacin.
    D. Pelvic floor exercises and tolterodine immediate release.

V. BENIGN PROSTATIC HYPERPLASIA

A. Epidemiology
    1. BPH usually develops after age 40.
    2. By age 60, 50% of all men have BPH; by age 85, 90% have BPH.

B. Pathophysiology and Clinical Presentation
    1. Type II 5-α-reductase facilitates conversion of testosterone to dihydrotestosterone, resulting in prostate growth.
    2. Lower urinary tract symptoms (LUTS) occur in 25% of men.
        a. Voiding (obstructive) symptoms: Decreased force, hesitancy, dribbling
        b. Storage (irritative) symptoms: Urinary urgency, frequency, nocturia, dysuria
    3. The American Urological Association Symptom Index (AUASI) score can help determine severity and appropriate treatment. The index consists of seven questions evaluating the severity of LUTS on a 0–5 scale. Higher numbers indicate more severe symptoms.

C. Evaluation
    1. Medical history, digital rectal examination, BUN, SCr, and urinalysis
    2. If prostate cancer is suspected, prostate-specific antigen (PSA)
    3. If significant urinary retention is suspected, need to assess PVR. If PVR is greater than 50 mL, patients have an increased risk of infection.
    4. Assess for medications that may exacerbate BPH symptoms.
        a. α-Adrenergic agonists (decongestants) can stimulate smooth muscle contraction in the prostate and urethra, obstructing urinary flow through the urethra.
        b. Anticholinergic drugs (urinary and GI antispasmodics, antihistamines, tricyclic antidepressants, phenothiazines) can reduce the ability of the bladder detrusor muscle to contract and empty the bladder.
        c. Diuretics can increase urinary frequency and volume.
        d. Testosterone replacement can stimulate prostate growth.
    5. If the AUASI score is 0–7 (mild), use watchful waiting.
    6. Patients with high AUASI scores of 20 and more (severe disease) should be assessed for prostatectomy.
    7. Patients with moderate disease (scores 8–19) are candidates for medical treatment.

D. Pharmacologic Treatment (Table 10)
   1. α-Adrenergic blockers: These relieve LUTS in men with moderate or severe AUASI scores by reducing smooth muscle contractions in the urethra and surrounding tissues.
      a. Nonspecific α-adrenergic blockers such as doxazosin and terazosin also lower blood pressure significantly.
      b. Newer agents are uroselective antagonists of α_1-adrenergic receptors (tamsulosin, silodosin) and selective antagonists of postsynaptic α_1-adrenergic receptors (alfuzosin) in the prostate and bladder. They may have less associated hypotension.
      c. All α-blockers can cause hypotension.
      d. Compared with placebo, α-blockers lower the AUASI score by 4–6 points in patients with LUTS and BPH.
      e. All α-blockers are metabolized through the CYP3A4 pathway and have drug interactions with strong CYP3A4 inhibitors and inducers.
      f. Intraoperative floppy iris syndrome is a concern with α-blockers, especially tamsulosin. Men with LUTS being offered α-blockers should be asked about planned cataract surgery. Men with planned cataract surgery should avoid starting α-blockers until their cataract surgery is completed. If already taking an α-blocker, patients need to inform his surgeon so that precautions can be taken.
   2. 5-α-Reductase inhibitors
      a. These agents prevent the conversion of testosterone to dihydrotestosterone, modify the disease course, and may reduce the risk of urinary retention and surgical interventions.
         i. Finasteride competitively inhibits type II 5-α-reductase and lowers prostatic dihydrotestosterone by 80%–90%.
         ii. Dutasteride is a nonselective inhibitor of both type I and II 5-α-reductase. Prostatic dihydrotestosterone production is quickly suppressed with this agent.
         iii. Despite these pharmacologic differences, finasteride and dutasteride did not differ in trials; both reduced prostate size.
      b. 5-α-Reductase inhibitors do not immediately reduce LUTS and should be reserved for use in men with a large prostate (more than 30 mL in volume or 40 g in weight). At least 6 months of therapy is usually needed for clinical benefit. Prostate size may be reduced by about 25% during this interval.
      c. PSA concentrations are used to monitor for prostate cancer. Because these agents lower PSA concentrations, a baseline PSA test is recommended before initiating α-reductase inhibitors.
      d. Long-term therapy with an α-reductase inhibitor can increase the risk of high-grade tumors of the prostate in healthy men without a history of prostate cancer.
   3. Phosphodiesterase type 5 inhibitors
      a. Tadalafil 5 mg once daily is approved for use in BPH.
      b. Mechanism is thought to be caused by phosphodiesterase-induced smooth muscle relaxation in the bladder, urethra, and prostate.
      c. Studied as monotherapy; the FDA does not recommend use in combination with α-blockers because the combination has not been adequately studied for BPH, and there is a risk of lowering the blood pressure. May be used in practice to treat both BPH and erectile dysfunction
   4. Combination therapy
      a. May be needed in men with LUTS, a larger prostate size, and an elevated PSA or in men with co-occurring symptoms of erectile dysfunction
      b. Finasteride and doxazosin are the best studied; dutasteride is FDA label approved for use with tamsulosin in symptomatic men having an enlarged prostate.
      c. Two large clinical trials (Medical Therapy of Prostatic Symptoms [MTOPS] and the Combination of Avodart and Tamsulosin studies [CombAT]) comparing monotherapy with combination therapy concluded that in men with LUTS and an enlarged prostate, further benefit can be achieved using the two drugs in combination.

5. Supplements
   a. Saw palmetto plant extract (*Serenoa repens*)
      i. Conflicting evidence about the efficacy of saw palmetto in relieving LUTS; 2012 systematic review suggested no benefit over placebo
      ii. Using this agent with 5-α-reductase inhibitors may reduce the efficacy of the reductase inhibitors.
   b. β-Sitosterol, *Pygeum africanum* show some benefit, but short-term studies
6. Management of storage (irritative) symptoms
   a. Anticholinergic or β_3-agonist agents can be appropriate and effective alternatives in men when LUTS are predominantly storage (irritative) symptoms, regardless of PVR.
7. Surgery is preferred in men with severe symptoms and in those with moderate symptoms who lack adequate response to medical options.

Table 10. Comparison of Pharmacologic Agents Used for Benign Prostatic Hyperplasia

Medication	Dose Range	Select Adverse Effects	Comments
Terazosin Doxazosin	1–10 mg daily 1–8 mg daily	Orthostatic hypotension	Initiate at low dose; can titrate every 2–7 days Start at bedtime
Alfuzosin ER	10 mg daily	Orthostatic hypotension	No need to titrate Take after a meal
Tamsulosin modified release	0.4–0.8 mg daily	May cause less orthostasis Causes ejaculatory dysfunction	Start at bedtime
Silodosin	8 mg daily 4 mg daily if CrCl 30–50 mL/min/1.73 m^2	Causes ejaculatory dysfunction; appears less sedating	Contraindicated if CrCl < 30 mL/min/1.73 m^2 Take with food
Finasteride Dutasteride Dutasteride/ tamsulosin	5 mg daily 0.5 mg daily 0.5/0.4 mg daily	Decreased libido	Onset of action is usually 6 mo Monitor PSA Pregnancy category X
Tadalafil	5 mg daily	Orthostatic hypotension	Avoid use with α-blockers No data in combination or with long-term use

PSA = prostate-specific antigen.

Patient Case

14. An 85-year-old man with LUTS visits his physician, who determines his AUASI score is 15. His blood pressure is 118/70 mm Hg sitting. A digital rectal examination confirms the diagnosis of BPH, and the physician schedules a further workup including a prostate ultrasound, which shows a prostate volume of 31 g. Which therapy is best at this time?

    A. Terazosin.

    B. Finasteride plus saw palmetto.

    C. Tamsulosin.

    D. Finasteride plus tamsulosin.

VI. OSTEOARTHRITIS

A. Epidemiology
   1. OA is the most prevalent form of arthritis, affecting more than 46 million Americans.
   2. Highly associated with aging: Large weight-bearing joints (e.g., hip and knee) are commonly affected.

B. Etiology and Pathophysiology
   1. Risk factors include age, female sex, obesity, genetics, sports activities, occupation, previous injury, acromegaly, and other chronic illnesses.
   2. Loss of cartilage occurs in the joint as the balance of chondrocyte function shifts from formation to destruction. Secondary inflammation and production of cytokines play a role.
   3. Subchondral bone and the synovium are damaged, and the joint space narrows.
   4. Single injuries or repeated micro-injuries may initiate or accelerate process.
   5. Symptoms of pain result from activation of nociceptive nerve endings in the damaged joint.
   6. Therapy goals: Relieve pain and swelling, maintain or improve joint function, prevent loss of function, and maintain or improve quality of life

C. Nonpharmacologic Treatment
   1. Patient education: Lifestyle, expectations, when to seek care, and behavioral, psychosocial, and physical interventions, including self-efficacy and self-management programs to reduce pain and disability
   2. Weight loss decreases the biomechanical load on large weight-bearing joints; even a small amount of weight loss helps decrease pain and disability.
   3. Exercise, including yoga, tai chi, weight bearing
   4. Physical and occupational therapy
   5. Surgery

D. Drug Therapy
   1. NSAIDs are first line; topical agents are preferred, particularly for knee OA, to reduce systemic exposure and adverse effects.
      a. Avoid chronic use, or if necessary, use a cyclooxygenase 2 (COX-2) selective NSAID or add a proton pump inhibitor to reduce the risk of GI bleeding. This recommendation is especially important for older adults.
      b. If one NSAID is not effective, change to others.
      c. Monitor for adverse effects: Rash, abdominal pain, GI bleeding, renal impairment, hypertension, heart failure, and drug-drug interactions
      d. Patients taking aspirin (for cardiac disease) should be educated to take aspirin at least 30 minutes before their first daily NSAID dose in the morning to avoid any interactions or reductions in aspirin efficacy. Naproxen appears to be safest with respect to cardiac risk.
      e. Monitor in chronic users: CBC, BUN, SCr, and AST at least annually
   2. Topical agents: Topical NSAIDs are preferred for knee OA or smaller joints near surface of skin. Limited efficacy for widespread joint pain
      a. Diclofenac 1% gel (or patch is FDA labeled for minor trauma): Four short-term trials showed a 50% reduction in pain in 40% of subjects (number needed to treat was 5); longer-term trials had number needed to treat of 10. Comparative trials with oral administration showed no difference in the proportion of patients who received pain relief.
      b. Topical capsaicin is conditionally recommended for knee OA and conditionally recommended against for hand OA; usually dosed four times daily on a scheduled basis, not as-needed; difficult to administer: Wear gloves, avoid contact with eyes, and do not skip doses. Local irritation occurs in 40% of patients.

   c. Use of topical rather than oral NSAIDs for patients 75 and older who have hand or knee OA may be preferred to reduce systemic absorption and adverse effects.
3. Intra-articular glucocorticoid injections:
   a. Methylprednisolone or triamcinolone 10- to 40-mg injection depending on size of joint; may be repeated every 3 months
   b. Primary adverse effects are risk of septic arthritis, synovitis
4. Acetaminophen:
   a. Alternative to NSAIDs or when NSAID use is contraindicated; very small effect sizes in clinical trials, few of those treated experience important benefit
   b. Maximum dosage of 3 g daily in divided doses should be considered in older adults with frailty or those 75 and older.
   c. Ensure the patient knows to watch for "hidden" acetaminophen in other products.
   d. Monitor for hepatotoxicity in patients with an elevated risk of liver disease (previous liver problems, heavy alcohol consumption) with periodic liver function tests. May consider limiting dosage to 2 g daily
5. Duloxetine
   a. Most of the evidence is in OA of knee, but conditionally recommended for patients with OA of knee, hip, or hand
   b. Can be used alone or in combination with NSAIDs
   c. Concerns about patient tolerability; use shared decision-making before initiation
6. Dietary supplements: Glucosamine-containing supplements are commonly used for relief of OA pain.
   a. 2019 American College of Rheumatology (ACR) guidelines strongly recommend against use of glucosamine supplements for relief of knee, hip, and/or hand OA.
   b. Chondroitin sulfate or combination glucosamine/chondroitin use is recommended against for knee and/or hip OA but is conditionally recommended for hand OA.
   c. Evidence to support treatment is contradictory; many studies are low quality.
   d. The adverse effect profile of glucosamine/chondroitin is similar to that of placebo.
7. Opioids
   a. Tramadol is an alternative when NSAIDs are ineffective or contraindicated; conditionally recommended for patients with knee, hand, and/or hip OA
   b. Non-tramadol opioids are conditionally recommended against in patients with knee, hand, and/or hip OA. However, they can be used in certain circumstances when non-opioid alternatives have been exhausted.
   c. Monitor and anticipate opioid adverse effects, and treat accordingly.

Patient Case

15. An 85-year-old man presents with pain from OA of the knee. He has hypertension, coronary artery disease, and BPH. For OA, he has been taking acetaminophen 650 mg three times daily. He reports that acetaminophen helps but that the pain persists and limits his ability to walk. Which is the best next step for this patient?

    A. Change acetaminophen to celecoxib.

    B. Add diclofenac gel to knee.

    C. Change acetaminophen to ibuprofen.

    D. Add duloxetine.

VII. RHEUMATOID ARTHRITIS

A. Epidemiology
   1. A systemic disease characterized by a bilateral inflammatory arthritis that usually affects the small joints of the hands, wrists, and feet
   2. The prevalence is estimated to be 1%–2%, with women predominating until after age 60, when prevalence becomes equal.
   3. RA can occur at any age but increases in prevalence up to age 70.
   4. RA is an autoimmune disease with a strong genetic predisposition.

B. Pathophysiology and Clinical Presentation
   1. Chronic inflammation of the synovium leads to proliferation and development of a pannus.
   2. The pannus invades joint cartilage and eventually causes erosion of the bone and joint destruction.
   3. The cause of the initial inflammatory activation is unknown, but once activated, the immune system produces antibodies and cytokines that accelerate cartilage and joint destruction.
   4. Patients present with joint pain and stiffness, fatigue, and other inflammatory symptoms. Symptoms also include warmth, redness, and swelling of the joints, usually with symmetrical distribution.
   5. Laboratory tests often show a positive RF, an elevated sedimentation rate, CRP, anti–cyclic citrullinated peptide antibodies, and normochromic normocytic anemia.
   6. RA can also affect other organs, causing pulmonary fibrosis, vasculitis, and dry eyes.

C. Treatment
   1. The treatment goal is to control the inflammatory process so that disease remission occurs. This leads to relief of pain, maintenance of function, and improved quality of life. Treatment response can be measured by:
      a. Reduction in the number of affected joints and in joint tenderness and swelling
      b. Improvement in pain
      c. Decreased amount of morning stiffness
      d. Reduction in serologic markers such as RF
      e. Improvement in quality-of-life scales
   2. Nonpharmacologic treatment: Concurrent with pharmacologic treatment
      a. Rest during periods of disease exacerbation
      b. Occupational and physical therapy to support mobility and maintain function
      c. Maintenance of a normal weight (avoid overweight and obesity) to reduce biomechanical stress on joints
      d. Assistive devices, if needed
      e. Surgery for tendons or joints
   3. Disease-modifying antirheumatic drugs (DMARDs)
      a. Initiate a DMARD within 3 months of diagnosis.
      b. Treatment strategies
         i. Treat-to-target
            (a) Frequent monitoring of disease activity using validated measures and modification of treatment to minimize disease activity
            (b) Initial goal is low disease activity, then remission
            (c) Based on optimization of methotrexate before adding or changing other DMARDs

ii. Tapering/discontinuing DMARDs
(a) Continuation of all DMARDs at current doses is recommended over a dose reduction or discontinuation, regardless of remission.
(b) Dose reduction or discontinuation may be considered on the basis of shared decision-making and patient preferences if the patient is at target (low disease activity or remission) for at least 6 months. Gradual dose reduction/taper is preferred to abrupt discontinuation.

c. Nonbiologic DMARDs are first line.
i. For DMARD-naive patients with moderate to high disease activity:
(a) Methotrexate preferred first line: Oral methotrexate preferred to subcutaneous because of ease of administration and similar bioavailability at starting doses
(b) Leflunomide can be considered alternative first line: Efficacy similar to methotrexate, but less long-term data and increased cost compared with methotrexate
(c) Hydroxychloroquine and sulfasalazine second line
ii. For DMARD-naive patients with low disease activity:
(a) Hydroxychloroquine recommended first line because of low adverse effect profile
(b) Sulfasalazine recommended over methotrexate and leflunomide: Sulfasalazine preferred in pregnancy
iii. Some patients with poor prognostic indicators such as functional limitation, extra-articular disease, positive RF, anti–cyclic citrullinated peptide antibodies, or bony erosions on radiography may be candidates for combination DMARD therapy.

d. Biologic DMARDs are used in combination with methotrexate for severe disease or as alternatives if nonbiologic DMARDs are ineffective or contraindicated.
i. Tumor necrosis factor (TNF) inhibitors: Etanercept, infliximab, adalimumab, certolizumab, golimumab
ii. Non-TNF biologics: Abatacept, anakinra, rituximab, tocilizumab, sarilumab
iii. Biologic kinase inhibitor: Tofacitinib, baricitinib, upadacitinib
iv. An FDA boxed warning was added in September 2021 for tofacitinib regarding increased risk of serious cardiac-related events such as a myocardial infarction or stroke, cancers, blood clots, and death according to the review of clinical trial safety results that compared tofacitinib with TNF inhibitors in patients with RA. Boxed warnings were also added to baricitinib and upadacitinib. Avoid in patients who currently smoke or formerly smoked, those with CV risk factors, and those with a known malignancy.
v. Most often used: Etanercept, infliximab, abatacept, or rituximab

4. Glucocorticosteroid and NSAID use in RA
a. Glucocorticosteroids have often been used as bridge therapy to provide anti-inflammatory effects while waiting for the DMARDs to take effect; however, this is no longer recommended because of the risk of adverse effects associated with glucocorticosteroids (osteoporosis, infection risk, CV disease [CVD]).
i. Initiation/addition/changing of DMARD without glucocorticosteroids is recommended over use of concomitant glucocorticosteroids.
ii. If glucocorticosteroids are required on the basis of patient-specific factors, short-term use (less than 3 months) is preferred to long-term use.
b. NSAIDs do not affect disease progression in RA; their anti-inflammatory effect occurs within 1–2 weeks of daily dosing, whereas the analgesic effect begins within several hours of administration.

D. Comorbid Conditions
   1. Patients with RA are more likely to develop other chronic diseases, either from the effects of RA or from the medications used to treat RA.
   2. CVD (myocarditis and heart failure) causes 40% of all deaths in patients with RA. Low-dose aspirin, omega-3 fatty acids, statins, or combination therapy should be considered.
      a. Follow standard guidelines to lower CV risk factors.
      b. In a patient with congestive heart failure, it is recommended to avoid TNF inhibitors.
   3. Infection risk is elevated, particularly in pulmonary infections and sepsis. A history of tuberculosis or hepatitis B calls for extra vigilance.
      a. Tuberculosis and viral hepatitis screening is required for patients who are considered for therapy with biologic DMARDs.
      b. Immunizations are best given before initiating DMARDs or biologics. A 2-week waiting period is recommended.
      c. Avoid live vaccines while the patient is taking DMARDs or biologics.
      d. Patients with hepatitis B or C, if treated with effective antivirals, are treated the same as patients without hepatitis; however, with untreated disease, DMARDs are preferred to TNF inhibitors.

Table 11. Selected DMARDs for RA

Drug	Customary Dose	Comments
Nonbiologic DMARDs		
Methotrexate	Initial: 15 mg weekly × 4–6 wk	First line for moderate to high RA disease activity; monitor for myelosuppression, liver dysfunction, and pulmonary fibrosis; a teratogen
Leflunomide (Arava)	10–20 mg/day	Similar to methotrexate; an initial loading dose may give therapeutic response within the first month
Hydroxychloroquine (Plaquenil)	200–300 mg twice daily	First line for low RA disease activity; must routinely monitor for ocular toxicity; however, this agent has a better adverse effect profile overall
Sulfasalazine	500–1000 mg twice daily	GI adverse effects often limit the use of this agent
Biologic DMARDs		
TNF Inhibitors		
Etanercept (Enbrel)[a]	50 mg SC weekly	Binds to TNF, inactivating this cytokine; generally well tolerated; usually used in those whose methotrexate therapy fails; monitor for infection; check baseline PPD
Infliximab (Remicade, biosimilar version)	3 mg/kg IV at 0, 2, and 6 wk; then every 8 wk thereafter	A mouse/human chimeric antibody to TNF; used in combination with methotrexate to prevent formation of antibodies to this protein; monitor for infection; check baseline PPD
Adalimumab (Humira)[a]	40 mg SC every 2 wk	Human antibody to TNF; less antigenic than other TNF antibodies; monitor for infection; check baseline PPD
Certolizumab pegol (Cimzia)	400 mg SC at 0, 2, and 4 wk; then 200 mg every other week	Monoclonal antibody against TNF; may have best response when used in combination with methotrexate Monitor for infections
Golimumab (Simponi)	50 mg SC every month	Monoclonal antibody against TNF Intended for use in combination with methotrexate Monitor for infections

Table 11. Selected DMARDs for RA *(Cont'd)*

Drug	Customary Dose	Comments
Non-TNF Biologics		
Abatacept (Orencia)	Weight-based dose at 0, 2, and 4 wk; then monthly (i.e., 750 mg for those weighing 60–100 kg)	Inhibit interactions between antigens and T cells; may be useful in those who do not respond to TNF inhibitors; monitor for infusion reactions
Anakinra (Kineret)	100 mg SC daily	IL-1 receptor antagonist; avoid combination therapy with TNF agents because of elevated risk of infection
Rituximab (Rituxan)[a]	Two infusions of 1000 mg given 2 wk apart	Chimeric antibody to CD20 protein on B lymphocytes; corticosteroid infusions help reduce infusion reactions; used in combination with methotrexate to improve response
Sarilumab (Kevzara)	200 mg SC once every 2 wk	IL-6 receptor antagonist May use as monotherapy or in combination with nonbiologic DMARDs Should not be used in combination with biologic DMARDs Do not initiate if ANC < 2000/mm^3, Plt < 150,000/mm^3, or ALT/AST > 1.5 times the ULN
Tocilizumab (Actemra)	4-mg/kg IV infusion every 4 wk; can increase to 8 mg/kg depending on clinical response	Anti–human IL-6 receptor monoclonal antibody; indicated for patients who have not responded to TNF inhibitors Monitor for infections
Kinase Inhibitors		
Baricitinib (Olumiant)	2 mg daily	Oral Janus kinase inhibitor May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs Not recommended for use with biologic DMARDs or potent immunosuppressants (azathioprine, cyclosporine) Do not initiate therapy with absolute lymphocyte count < 500 cells/mm^3, ANC < 1000 cells/mm^3, or Hgb < 8 g/dL. Boxed warning (mentioned above)
Tofacitinib (Xeljanz)	5 mg twice daily	Oral Janus kinase inhibitor; intended as second-line therapy Can be used as monotherapy or in combination with methotrexate. Boxed warning (mentioned above)
Upadacitinib (Rinvoq)	15 mg daily	Oral Janus kinase inhibitor May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs Not recommended for use with biologic DMARDs or potent immunosuppressants Do not initiate therapy with absolute lymphocyte count < 500 cells/mm^3, ANC < 1000 cells/mm^3, or Hgb < 8 g/dL. Boxed warning (mentioned above)

[a]Biosimilar available.

ANC = absolute neutrophil count; DMARD = disease-modifying antirheumatic drug; IL = interleukin; IV = intravenous(ly); PPD = purified protein derivative; RA = rheumatoid arthritis; SC = subcutaneous(ly); TNF = tumor necrosis factor; ULN = upper limit of normal.

4. Malignancy is more common, particularly GI cancers and lymphoproliferative disorders. In addition, melanoma and lung cancer rates were elevated in one cohort study. Use DMARDs over biologics in melanoma; use rituximab over TNF inhibitors in lymphoproliferative disorders.
5. Osteoporosis is more common in patients with RA. Calcium and vitamin D are recommended. In addition, bisphosphonates should be considered for prevention if prednisone 5 mg or more daily is prescribed.

Patient Case

16. A 65-year-old woman was diagnosed with RA 1 year ago. At that time, her RF titer was 1:64; she presented with joint inflammation in both hands and about 45 minutes of morning stiffness. She began therapy with oral methotrexate and currently receives methotrexate 15 mg weekly, folic acid 2 mg daily, ibuprofen 800 mg three times daily, and omeprazole 20 mg daily. At today's clinic visit, the patient reports the recurrence of her symptoms. Radiographic evaluation of her hand joints reveals progression of joint space narrowing and bone erosion. Which is the next best step for treating this patient's RA?

    A. Add etanercept.

    B. Change to leflunomide.

    C. Add prednisone bridge therapy.

    D. Change to hydroxychloroquine.

VIII. GOUT

A. Definition: A spectrum of clinical and pathologic features caused by hyperuricemia (SU concentrations more than 6.8 mg/dL) resulting in tissue deposition of monosodium urate monohydrate crystals in the extracellular fluid of joints and other sites
    1. Most common form of inflammatory arthritis; prevalence estimated at 9.2 million adults (3.9%) in the United States
    2. Characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain, called acute gouty arthritis, acute gout attacks, or acute gout flares
    3. Also known as monosodium urate crystal deposition disease

B. Diagnosis
    1. Typically presents as acute episodic arthritis
    2. May also present as chronic arthritis of one or more joints, particularly if prolonged hyperuricemia exists
    3. Tophi may be present; detected on physical examination or with imaging
    4. Renal manifestations include uric acid nephrolithiasis and chronic nephropathy.
    5. Features of acute gout attack include:
        a. Severe pain, redness, swelling; maximum severity in 12–24 hours; may continue for a few days to several weeks
        b. Most often affect the lower extremities in a single joint
            i. Most common joint: First metatarsophalangeal joint (podagra) or knee
            ii. May occur in many other joints, including those of upper extremities
            iii. May be polyarticular at first presentation (less than 20% of cases)

6. Ideally, definitive diagnosis should be made by visualization of monosodium urate crystals under polarized compensated light microscopy in fluid aspirated from the affected joint during an acute gout attack.
    a. In the diagnosis of gout, monosodium urate crystals are negatively birefringent (needle shaped or rods).
    b. In pseudogout, crystals are calcium pyrophosphate dihydrate and are weakly positively birefringent (rods or rhomboidal).
    c. Diagnosis by joint aspiration is difficult because patients are in severe pain and often refuse joint aspiration during an acute attack. In this case, a provisional diagnosis can be made on the basis of clinical data.
7. If diagnosis by joint aspiration is not possible, a tentative diagnosis can be made by a combination of presentation or clinical picture and increased uric acid. Use of hyperuricemia as one of the criteria for diagnosing gout may be difficult during an initial acute attack because serum uric acid may be low during flares. The best time to check uric acid is 2 weeks after a flare.

C. Predisposing Factors
1. Dietary: High meat and seafood consumption, fatty foods, dietary overindulgence, high intake of beer and spirits (not wine) in men, sugar-sweetened soft drinks, high-fructose foods
2. Drugs: Thiazides and loop diuretics, niacin, calcineurin inhibitors, low-dose aspirin. During initiation of therapy, xanthine oxidase inhibitors (XOIs) and uricosuric agents may increase uric acid and symptoms.
3. Medical conditions and other factors: Obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, congestive heart failure, organ transplantation, renal insufficiency, early menopause, trauma, surgery, starvation, dehydration, episodic alcohol consumption

D. Classification
1. Four stages of gout:
    a. Asymptomatic
    b. Acute gouty arthritis
    c. Intercritical gout (intervals between attacks)
    d. Chronic recurrent gout
2. Severities of chronic tophaceous gouty arthropathy (CTGA)
    a. Mild: One joint, stable disease
    b. Moderate: Two to four joints, stable disease
    c. Severe
        i. CTGA of more than four joints *or*
        ii One or more unstable, complicated, severe articular tophi
    d. Size of joints
        i. Large joints (e.g., knee, ankle, wrist, elbow, hip, shoulder)
        ii. Medium joints (e.g., wrist, ankle, elbow)
        iii. Small joints (e.g., interphalangeal)

E. Treatment Goals
1. The minimum SU target is less than 6 mg/dL.
2. An SU target of 5 mg/dL or less may be needed to improve gout signs and symptoms. Consider a goal of 5 mg/dL or less if tophi are present.
3. Decrease the frequency of acute gout attacks.

F. Nonpharmacologic Therapy (Table 12)

Table 12. Nonpharmacologic Therapy for Gout[a]

Lifestyle and General Health		
Weight loss if obesity Healthy overall diet Exercise Smoking cessation Proper hydration		
Foods and Drinks to Avoid	**Foods and Drinks to Limit**	**Foods and Drinks to Encourage**
Organ meats high in purines (e.g., liver, kidney, sweetbreads)	Serving sizes of: Beef, lamb, pork Seafood with high purine content (e.g., sardines, shellfish)	Low- or nonfat dairy products
High-fructose corn syrup–sweetened sodas, beverages, and foods	Servings of naturally sweet fruit juices Table sugar, sweetened beverages, desserts Table salt	Vegetables
Alcohol overuse (> 2 per day for men, > 1 per day for women) in all patients Any alcohol use during times of frequent gout attacks or advanced gout under poor control	Alcohol (particularly beer, but also wine and spirits)	

[a]Note: These approaches are based on a paucity of high-quality evidence on the effects of dietary and lifestyle factors for reducing the risk of recurrent gout attacks./

Adapted from: Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1. Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.

G. Treatment of Acute Gout (Table 13)
   1. Assess severity of gout attack (Table 14), and select treatment accordingly.
   2. Initiate pharmacologic treatment within 24 hours of onset of an acute gout attack. Colchicine is appropriate only if initiated within 36 hours of attack onset.
   3. Continue established urate-lowering therapy (ULT) without interruption during an acute gout attack (do not discontinue ULT).
   4. Consider oral colchicine, NSAIDs, or glucocorticoids (oral, intra-articular, or intramuscular) as appropriate first-line agents for gout flares.
      a. Colchicine, NSAIDs, or glucocorticoids should be chosen according to patient factors and preferences.
      b. When colchicine is chosen, low dose is recommended over high dose, given its similar efficacy and more favorable adverse effect profile. FDA-approved dosing should be followed: 1.2 mg immediately, followed by 0.6 mg 1 hour later with ongoing anti-inflammatory therapy until the flare resolves.
      c. For patients with nothing-by-mouth status, glucocorticoids (intramuscular, intravenous, or intra-articular) are recommended over interleukin-1 (IL-1) inhibitors or ACTH (adrenocorticotropic hormone).

Table 13. Medication Dosing for Acute Gout Attack

Drug	Dose	Comments
Colchicine (Colcrys)	First day: 1.2 mg, then 0.6 mg 1 hr later; day 2 and thereafter: 0.6 mg twice daily until flare resolves CrCl 30–80 mL/min/1.73 m^2: Monitor for adverse effects; dose adjustment not necessary CrCl < 30 mL/min/1.73 m^2: Dose adjustment not necessary but may be considered; do not repeat course of treatment more often than every 2 wk Dialysis: 0.6-mg single dose; do not repeat course of treatment more often than every 2 wk Severe hepatic impairment: Dose reduction not necessary but may be considered; do not repeat course of treatment more often than every 2 wk	Concomitant use with P-gp inhibitors or strong CYP3A4 inhibitors is contraindicated in renal or hepatic impairment (fatal toxicity has occurred) Colchicine dose should be reduced if renal and hepatic function normal and if used concomitantly with P-gp inhibitors or moderate to strong CYP3A4 inhibitors
NSAIDs	Naproxen: 750 mg initially, followed by 250 mg every 8 hr Naproxen ER: 1000–1500 mg once daily, followed by 1000 mg once daily Indomethacin: 50 mg three times daily until pain is tolerable; then reduce dose until attack resolves Sulindac: 200 mg twice daily Use anti-inflammatory or analgesic doses of other NSAIDs, same as for treatment of acute pain or inflammation	The only FDA-approved NSAIDs are naproxen, indomethacin, and sulindac; however, other NSAIDs may be as effective Continue full dose until attack completely resolves Can taper dose if comorbidities or renal or hepatic impairment is present
Celecoxib (Celebrex)	800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for 1 wk	Only in certain patients when NSAIDs are contraindicated or not tolerated
Glucocorticoids	Prednisone 0.5 mg/kg per day for 5–10 days *or* Prednisone 0.5 mg/kg per day for 2–5 days, then taper for 7–10 days, then discontinue *or* Methylprednisolone dose pack Option for one or two large joints: Intra-articular corticosteroids Dose according to the size of the joint (e.g., triamcinolone 40 mg for large joint, 30 mg for medium joint, 10 mg for small joint or equivalent) IM triamcinolone 60 mg, followed by oral glucocorticoid (dosing as above)	Intra-articular corticosteroids may be used in combination with OCSs, NSAIDs, or colchicine

IM = intramuscular(ly); OCS = oral corticosteroid; P-gp = P-glycoprotein.

Table 14. Severity, Duration, and Extent of Acute Gout Attacks

Severity[a]	
Mild	≤ 4
Moderate	5 or 6
Severe	≥ 7
Duration Since Onset	
Early	< 12 hr after attack onset
Well established	12–36 hr after attack onset
Late	> 36 hr after attack onset
Extent	
One or a few small joints	
One or two large joints	Large joints: Ankle, knee, wrist, elbow, hip, shoulder
Polyarticular	≥ 4 joints involving > 1 region (regions: forefoot, midfoot, ankle or hindfoot, knee, hip, fingers, wrist, elbow, shoulder) Three separate large joints

[a]Self-reported; based on a 0–10 visual analog scale.

H. Management of Hyperuricemia – Chronic ULT (Table 15)
   1. Consider discontinuing nonessential medications that cause hyperuricemia.
   2. Recognize indications for chronic ULT:
      a. Strongly recommend for patients with:
         i. One or more subcutaneous tophi on clinical examination or imaging study
         ii. Two or more acute gout attacks per year
         iii. Radiographic damage as a result of gout
      b. Conditionally recommend for patients with: First gout flare AND history of stage 3 or higher chronic kidney disease (CKD), SU greater than 9 mg/dL, or urolithiasis
      c. Recommend against for patients with:
         i. First gout glare
         ii. Asymptomatic hyperuricemia (SU greater than 6.8 mg/dL) with no prior gout flares or subcutaneous tophi
   3. Initiating ULT
      a. ULT initiation recommended during acute gout flare over waiting until flare resolution
      b. First line: XOIs
         i. Allopurinol is the preferred first-line agent for all patients, including those with moderate to severe stage 3 or higher CKD. Start at a low dose (100 mg/day or less) with dose titration to target SU over starting at a higher dose.
            (a) Allopurinol hypersensitivity syndrome is possible.
               (1) Highest risk during the first few months of therapy
               (2) Manifestations: Stevens-Johnson syndrome, toxic epidermal necrolysis, clinical constellation of symptoms (eosinophilia, rash, vasculitis, major end-organ disease)
               (3) Risk factors: Concomitant thiazide diuretics, renal impairment
            (b) Testing for *HLA-B*5801* is only recommended in patients of African American or Southeast Asian descent.
         ii. Change to alternative XOI (e.g., febuxostat of 40 mg/day or less) in patients intolerant of or refractory to first XOI.

c. Alternative: Uricosuric agent
    i. A uricosuric if at least one XOI is contraindicated or not tolerated
    ii. Probenecid 500 mg once or twice daily with dose titration recommended over higher doses
d. Last line: Pegloticase
    i. If the goal SU is still not achieved and patients continue to have frequent gout flares (2 flares/year or more) despite XOI and uricosuric therapy, discontinue other therapies and change to pegloticase.
    ii. Pegloticase is not recommended for first-line therapy in any case.

4. Initiate anti-inflammatory prophylaxis for acute gout concomitantly with or just before ULT in all patients.
    a. There may be an early increase in acute gout attacks during ULT initiation.
        i. May be caused by rapid decrease in urate concentrations, resulting in remodeling of articular urate crystal deposits
        ii. Patient education is crucial; lack of education may increase the risk of nonadherence to ULT.
    b. Colchicine, NSAIDs, prednisone/prednisolone may be chosen on the basis of patient-specific factors and preferences
    c. Continue anti-inflammatory prophylaxis for 3–6 months, with ongoing evaluation.
    d. Continue anti-inflammatory prophylaxis beyond 6 months in the presence of any clinical evidence of gout disease activity (tophi, recent flare, chronic gouty arthritis).
5. Treat-to-target management
    a. Recommended: Treat-to-target management strategy of ULT by achieving and maintaining SU at less than 6 mg/dL rather than fixed-dose strategy
    b. Augmented treat-to-target protocol of ULT dose management by nonphysician providers (e.g., nurses and pharmacists) is recommended when resources are available.

Table 15. Chronic ULT

Drug	Dose	Comments
Allopurinol (Zyloprim)[a]	Starting dose: 100 mg daily (50 mg daily in stage 4 CKD) Gradually titrate dose every 2–5 wk to appropriate maximum dose (800 mg daily with normal renal function) or until goal urate concentration reached Maintenance dose can be > 300 mg daily, even in CKD, as long as patient is educated and regular monitoring occurs for hypersensitivity, rash, pruritus, elevated hepatic enzymes, and eosinophilia	XOI Low starting dose reduces early gout flares and risk of hypersensitivity syndrome Consider keeping dose lower in CKD and not increasing to maximum dose; data with dosing > 300 mg/day in CKD are limited Dose reduction algorithms in CKD have been developed but are not evidence based; the ACR guidelines do not recommend following them
Febuxostat (Uloric)[a]	Starting dose: 40 mg once daily May increase dose to 80 mg once daily if goal SU not reached CrCl < 30 mL/min/1.73 m^2: Use caution; insufficient data	XOI FDA black box warning: Increased risk of CV death compared with allopurinol

Table 15. Chronic ULT *(Cont'd)*

Drug	Dose	Comments
Probenecid (generic only)[a]	Starting dose: 250 mg twice daily × 1 wk May increase weekly in 500-mg/day increments to maximum dose of 1 g twice daily, if needed Avoid if CrCl < 30 mL/min/1.73 m^2	Uricosuric; alternative agent after XOI
Pegloticase (Krystexxa)[a]	8 mg IV every 2 wk No dose adjustment for CKD	Use only if severe gout disease burden *and* refractory to or intolerant of other ULT options All other antihyperuricemic agents must be discontinued before initiation of pegloticase; do not administer concomitantly Premedicate with antihistamines and corticosteroids

[a]Always initiate concomitant prophylactic therapy.

CKD = chronic kidney disease; CV = cardiovascular; IM = intramuscular(ly); IV = intravenous(ly); P-gp = P-glycoprotein; PUD = peptic ulcer disease; SU = serum urate; ULT = urate-lowering therapy; XOI = xanthine oxidase inhibitor.

Table 16. Medications for Chronic Urate-Lowering Therapy and Acute Gout Attack Prophylaxis

Drug	Dose	Comments
Colchicine (Colcrys)	0.6 mg once or twice daily (maximum 1.2 mg daily) CrCl 30–80 mL/min/1.73 m^2: Monitor for adverse effects; dose adjustment not necessary CrCl < 30 mL/min/1.73 m^2: Initial dose 0.3 mg/day; use caution and monitor if dose titrated further Dialysis: 0.3 mg twice weekly; monitor for adverse effects Severe hepatic impairment: Dose reduction not necessary but may be considered; do not repeat course of treatment more often than every 2 wk	Concomitant use of colchicine with P-gp inhibitors or strong CYP3A4 inhibitors is contraindicated in renal or hepatic impairment (fatal toxicity has occurred) Colchicine dose should be reduced if renal and hepatic function normal and if used concomitantly with P-gp inhibitors or moderate to strong CYP3A4 inhibitors
NSAIDs	Lower doses than used for acute attacks (e.g., naproxen 250 mg twice daily, indomethacin 25 mg twice daily)	Consider concomitant proton pump inhibitor or other agent for suppression of PUD, when indicated
Oral glucocorticoids	Prednisone or prednisolone ≤ 10 mg daily	Consider, particularly if colchicine and NSAIDs are both contraindicated, ineffective, or not tolerated

P-gp = P-glycoprotein; PUD = peptic ulcer disease.

Patient Cases

Questions 17–19 pertain to the following case.

A 60-year-old man (weight 80 kg) presents with his third gout attack of the past year. His last attack, for which he took colchicine with good response, was 10 days ago. He is experiencing pain in his left knee and in the third and fourth proximal interphalangeal joints on his left hand. The pain started about 10 hours ago. The patient rates his pain as 6/10. He has chronic obstructive pulmonary disease and dyslipidemia, and his renal function is normal. His uric acid concentration 1 month ago was 10 mg/dL. He has no tophi. His only medications are inhaled tiotropium, albuterol, and simvastatin.

17. Which is most appropriate for treatment of this acute gout attack?
    A. Naproxen 750 mg, then 250 mg every 8 hours.
    B. Colchicine 1.2 mg, then 0.6 mg in 1 hour, then 0.6 mg every 12 hours.
    C. Intra-articular triamcinolone injection of all affected joints.
    D. Prednisone 40 mg daily plus naproxen 750 mg, then 250 mg every 8 hours.

18. Assuming this patient will be receiving acute anti-inflammatory therapy, which decision is most appropriate regarding ULT?
    A. Probenecid should be initiated, but treatment should be delayed until after the acute attack has resolved.
    B. Probenecid should be initiated and can be initiated during the acute attack.
    C. Allopurinol should be initiated, but treatment should be delayed until after the acute attack has resolved.
    D. Allopurinol should be initiated and can be initiated during the acute attack.

19. Which regimen for anti-inflammatory prophylaxis with ULT is most appropriate for this patient once the acute attack has resolved?
    A. Colchicine 0.6 mg daily.
    B. Prednisone 10 mg daily.
    C. Colchicine 0.6 mg daily plus naproxen 250 mg twice daily.
    D. Pegloticase 8 mg intravenously every 2 weeks.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

Renal elimination is usually the most significantly changed pharmacokinetic value in older adults. This patient's advanced age and diseases will add to her loss of renal function. Using the Cockcroft-Gault equation, this patient's estimated CrCl is 24 mL/minute/1.73 m^2. Creatinine clearance = $[(140 - 85) \times 65]/[(72 \times 1.8)] \times 0.85$. At this level of function, glyburide elimination would be prolonged, and metformin use is contraindicated (Answer D is correct). The aspirin is low dose, and melatonin is safe, even at very high doses (Answer A is incorrect). Although lisinopril is renally eliminated, dosing is based on response, and meclizine has mainly hepatic metabolism with no dosage adjustment in renal insufficiency (Answer B is incorrect). Lisinopril, unlike glyburide, is not considered potentially inappropriate in older adults (Answer C is incorrect).

2. Answer: B

Common pharmacodynamic changes associated with aging include impaired homeostasis for electrolytes with angiotensin-converting enzyme inhibitors such as lisinopril and increased sensitivity to anticholinergic adverse effects from drugs such as meclizine (Answer B is correct). Metformin and glyburide (and lisinopril in addition to its pharmacodynamic issues) have primarily pharmacokinetic issues because of renal excretion changes when used in older adults (Answers C and D are incorrect). Melatonin is extremely safe without pharmacodynamic or pharmacokinetic issues in older adults, and this patient's aspirin is low dose, so issues with GI bleeding are less than with higher doses (Answer A is incorrect).

3. Answer: A

Glipizide and simvastatin are not listed in the 2019 AGS Beers Criteria tables (Answer B is incorrect). In addition to glipizide not being listed, the patient's CrCl is greater than 30 mL/minute/1.73 m^2, and nitrofurantoin is not for long-term suppression of bacteria (Answer C is incorrect). Histamine-2 receptor antagonists are no longer recommended to avoid in patients with dementia or cognitive impairment because of weak evidence of adverse cognitive effects, and neither metoprolol nor clopidogrel is listed (Answer D is incorrect). However, paroxetine should be used with caution in patients with hyponatremia; donepezil as a CI should be avoided in patients with syncope because it can cause bradycardia; and tolterodine has strong anticholinergic properties and should be avoided in patients with dementia (Answer A is correct).

4. Answer: B

Fluticasone/salmeterol meets the 10 criteria for the Medication Appropriateness Index (Answer A is incorrect). Ranitidine has no listed indication in this patient, clopidogrel has exceeded the recommended therapy duration for her stent, and metoprolol has a significant drug-drug interaction with donepezil, given her bradycardia (Answer B is correct). Minus duplication with other drugs (clopidogrel), aspirin meets the other nine criteria of the Medication Appropriateness Index (Answer C is incorrect). Nitrofurantoin has been initiated for a presumptive UTI, given her history of frequent UTIs, and simvastatin is appropriate for her disease and condition (Answer D is incorrect).

5. Answer: C

Because the patient's A1C is less than 7.5%, glipizide should be reevaluated; donepezil use in dementia requires periodic reassessment of risk-benefit; and asymptomatic bacteriuria should not be treated with antimicrobials; these medications should be evaluated for continued need and possible discontinuation, according to the Choosing Wisely criteria (Answer C is correct). Paroxetine, ranitidine, and tolterodine are not addressed by these criteria (Answer A is incorrect). Similarly, metoprolol, clopidogrel, and tolterodine are not addressed by these criteria (Answers B and D are incorrect).

6. Answer: D

This patient had a geriatric syndrome (a fall) and hazards of hospitalization (decline in organ systems and function) that occur with many older adult patients. At this time, she has several risk factors for another fall, including a history of falls, diseases such as diabetes and hypertension, dizziness, and use of several drugs. An assessment of gait and balance would help determine the severity of her risk (Answer D is correct). Although the IADL assessment is overall good and functional, it does not focus on the risks associated with increased falls (Answer A is incorrect). Evaluating the presence or severity of depression or of pressure sores would not

be a functional assessment, though it would affect functional abilities (Answers B and C are incorrect).

7. Answer: C
Efforts to maintain bone and muscle strength are more important for this patient than primary prevention of CVD with atorvastatin or lisinopril. Most older adults do not consume a diet rich in vitamin D; moreover, most older adults have less sun exposure and are more likely to have a deficiency in vitamin D, which is a risk factor for falls and reduced muscle strength. Furthermore, naproxen is not a good alternative for the patient because of increased risk of GI bleeding and worsening renal function (Answer C is correct). Although simvastatin and lisinopril can prevent complications caused by CVD after extended use, they do not improve functional abilities in the short term (Answers A and B are incorrect). Pain management is important for functional status, but use of opioids compared with non-opioids has not been associated with differences in functional status (Answer D is incorrect).

8. Answer: B
This patient has a positive screen for mild dementia. However, when evaluating her cognitive loss, it is important to limit the use of any drug that could contribute to confusion, such as those identified on the AGS Beers Criteria, before treating for an unconfirmed condition (Answer A is incorrect). Anticholinergics such as tolterodine can cause confusion, so it would be best to discontinue this agent and reassess cognition before treating for AD (Answer B is correct). In addition, before initiating vitamin B_{12} injections, the patient should have laboratory evidence of deficiency (Answer C is incorrect). Without a serum sodium concentration, there is no reason to expect that hydrochlorothiazide would cause her cognitive decline, so changing to lisinopril is not indicated at this time (Answer D is incorrect).

9. Answer: B
Rivastigmine is a potent inhibitor of acetyl and butyryl cholinesterase, leading to significant cholinergic adverse effects such as nausea, vomiting, and diarrhea. However, use of the transdermal delivery system generates even plasma concentrations and lessens the incidence of cholinergic adverse effects. Because the maintenance dose has been achieved with rivastigmine 12 mg, this patient can change to the patch that delivers 9.5 mg/day (Answer B is correct). Antacids will not substantially alleviate the GI effects of CIs, and prochlorperazine is anticholinergic (Answers A and D are incorrect). Because rivastigmine appears to work, it is better to continue its use, if possible, than to change to memantine (Answer C is incorrect).

10. Answer: B
Over 3 years, this patient's MMSE score has decreased by only 4 points, which suggests a treatment response to donepezil. Furthermore, the patient can still live at home with her husband, and she has maintained some function in her basic ADLs. However, she has not responded to a higher donepezil dose, and there is no evidence that retrying it later is useful (Answer A is incorrect). Changing from one CI to another is not effective (Answer D is incorrect). Because she has benefited from donepezil use, she should not abruptly discontinue it. Some clinical trials with memantine show an additional treatment response when memantine is added to donepezil therapy. When the benefits, risks, and costs have been openly discussed and the family prefers to consent to therapy, a time-based trial is reasonable. Memantine should be initiated at 5 mg daily (Answer B is correct). Donepezil can be evaluated for tapering after memantine titration. Aducanumab is indicated for MCI or mild AD. An MMSE score of 17/30 indicates moderate dementia, disqualifying this patient for aducanumab use (Answer C is incorrect).

11. Answer: C
Patients in the late stages of dementia (as evidenced by an MMSE score of 5/30) with behavior issues would benefit most from nonpharmacologic treatment such as music therapy (Answer C is correct). Social isolation would likely increase symptomatology, and haloperidol is not recommended until nonpharmacologic treatments have failed or patients have become a harm to themselves or others. In addition, the haloperidol dose is excessive, with risk outweighing benefit (Answers B and D are incorrect). Although pain control may be useful, ibuprofen is not the first drug of choice and has more risk of harm than benefit in an older adult patient with frailty (Answer A is incorrect).

12. Answer: C
Increasing the dose of a CI has not been shown to reduce agitation with dementia (Answer A is incorrect). The patient has become a harm to self (because of refusing

care), so a course of quetiapine is appropriate, assuming other nonpharmacologic treatments have been tried unsuccessfully (Answer C is correct). Citalopram has small studies showing evidence of effectiveness in the literature, but its role in therapy for agitation is unclear (Answer D is incorrect). No sleep disturbance is noted, so melatonin is unlikely to help (Answer B is incorrect).

13. Answer: C

This patient has symptoms of urge incontinence. Pelvic floor exercises in conjunction with drug therapy should be offered for initial therapy (Answer C is correct). Darifenacin alone is not the best treatment (Answer B is incorrect). Some evidence indicates that solifenacin, a selective muscarinic blocker, does not worsen cognition, and solifenacin would be preferred to tolterodine in this patient with MCI (Answer D is incorrect). Mirabegron, a newer agent with less evidence for its exact role in therapy, should not be offered without pelvic floor exercises (Answer A is incorrect).

14. Answer: C

Pharmacologic therapy targeted at reducing urethral sphincter pressure has proved effective in reducing BPH symptoms. Tamsulosin is an α-adrenergic blocker with more specific activity for the genitourinary system. Given that the patient already has low normal blood pressure, tamsulosin would be preferred to terazosin (Answer C is correct; Answer A is incorrect). Orthostatic hypotension can still occur with all α-adrenergic blockers, so patients should be monitored when therapy is initiated. Finasteride, a 5-α-reductase inhibitor, and combination therapy with 5-α-reductase inhibitors are recommended when there is evidence of a large prostate (Answer D is incorrect). Saw palmetto is not recommended in combination with 5-α-reductase inhibitors because it may reduce their efficacy (Answer B is incorrect).

15. Answer: B

Topical NSAIDs are recommended first line for OA treatment, especially of small joints like the knee (Answer B is correct). Because of risks of GI bleeding and renal impairment, oral NSAIDs and COX-2 inhibitors may be considered when topical NSAIDs fail; however, they are not recommended for chronic use (Answers A and C are incorrect). Duloxetine may be considered for OA of the knee when first-line treatments fail; however, it will not provide immediate pain relief (Answer D is incorrect).

16. Answer: A

This woman has indicators of a poor prognosis with RA (positive RF, many symptoms) and has not responded to optimized methotrexate therapy. Although the next treatment step is not entirely clear, the best choices are between double- or triple-combination DMARD therapy and a biologic agent. Leflunomide or hydroxychloroquine would not be recommended as monotherapy for someone who has not responded to methotrexate (Answers B and D are incorrect). Etanercept has a response in 60%– 75% of patients whose methotrexate therapy has failed (Answer A is correct). Glucocorticosteroids are no longer recommended as adjunctive therapy and is inappropriate at this time (Answer C is incorrect).

17. Answer: A

Colchicine, corticosteroids, and NSAIDs are all appropriate first-line therapy for acute gout, making naproxen appropriate in this patient (Answer A is correct). Colchicine would not be recommended for this patient because he took acute colchicine doses in the past 2 weeks (Answer B is incorrect). Intra-articular corticosteroids are recommended only if only one or two large joints are affected (Answer C is incorrect). Because of this patient's acute gout attack of moderate severity, combination therapy is not recommended at this time (Answer D is incorrect).

18. Answer: D

Xanthine oxidase inhibitors like allopurinol are recommended first line for ULT and can be initiated during the acute attack if the patient is also receiving anti-inflammatory prophylaxis (Answer D is correct; Answer C is incorrect). Probenecid is second line if XOIs are contraindicated or not tolerated (Answers A and B are incorrect).

19. Answer: A

Oral low-dose colchicine is first line for anti-inflammatory prophylaxis with ULT (Answer A is correct). Oral glucocorticoids are associated with significant risks in long-term therapy and should not be used for anti-inflammatory prophylaxis unless both colchicine and NSAIDs are contraindicated, not tolerated, or ineffective (Answer B is incorrect). Combination therapy is not recommended for anti-inflammatory prophylaxis, (Answer C is incorrect). Pegloticase is used last line for ULT, not anti-inflammatory prophylaxis (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A
Diazepam is a long-acting benzodiazepine that can accumulate in older patients, resulting in excessive lethargy, sedation, and unsteady gait, and the patient admits taking it every night during the past week (Answer A is correct). Worsening of the patient's depression is evident with the recent bereavement; however, that would not explain the unsteady gait (Answer D is incorrect). Although metoprolol can cause lethargy, the patient's current blood pressure and metoprolol's β_1-selective nature would make metoprolol the unlikely cause of this new change in lethargy and unsteady gait (Answer B is incorrect). Atorvastatin is not a common cause of lethargy and confusion (Answer C is incorrect).

2. Answer: C
Because of slowed liver metabolism in older adults, accumulation of several active metabolites can be expected, leading to an increased risk of sedation and falls (Answer C is correct). Diazepam is converted to active metabolites nordiazepam, temazepam and oxazepam through CYP3A4. In older patients, the volume of distribution of lipid-soluble drugs such as diazepam is increased, not decreased (Answer D is incorrect). Oral absorption is not significantly altered in older adults for chronic medications (Answer A is incorrect). Decreased renal excretion is likely, but given the drugs on the patient's medication list, is not a significant contributor in him (Answer B is incorrect).

3. Answer: B
Adding vitamin D to this resident's regimen, given her deficient serum concentrations, may help reduce falls (Answer B is correct). Insufficient information is provided to determine the need to add memantine at this time (Answer A is incorrect). Aducanumab is currently only approved for MCI or mild AD; with an MMSE score of 16/30, the patient would be considered to have moderate dementia and would not qualify for aducanumab (Answer C is incorrect). Adding calcium carbonate might help reduce fractures but would not reduce fall risk (Answer D is incorrect).

4. Answer: D
Nonsteroidal anti-inflammatory drugs are recommended first line for patients with OA. For patients older than 75 with OA of the knee, topical NSAIDs are preferred to systemic NSAIDs because of lower risk of systemic adverse effects (Answer D is correct; Answer A is incorrect). A trial of acetaminophen at doses less than 3 g/day is reasonable for frail older adults with OA of the knee after a trial of a topical NSAID has failed (Answer B is incorrect). Tramadol at doses less than 200 mg/day would be a reasonable alternative when more conservative medications have failed a trial of 1–2 weeks (Answer C is incorrect).

5. Answer: D
All CIs have similar efficacy. The rivastigmine transdermal patch is better tolerated than oral rivastigmine, and 4.6 mg is the appropriate initial starting dose of the transdermal patch (Answer D is correct). Although donepezil tends to be the best-tolerated CI, doses of cholinesterase medications should be titrated slowly to prevent GI upset. The initial donepezil dose is 5 mg daily at bedtime and, for galantamine ER, 8 mg once daily (Answers A and B are incorrect). Memantine has no beneficial effect in maintaining cognitive function, as measured by MMSE scores (Answer C is incorrect).

6. Answer: A
This patient's current fasting blood glucose of 65 mg/dL and A1C of 5.6% should prompt the pharmacist to request glipizide discontinuation (Answer A is correct). According to the American Diabetes Association's Standards of Medical Care in Diabetes guidelines, older adults with several chronic illnesses, cognitive impairment, or functional dependence should have less-stringent glycemic goals, such as A1C less than 8.0%–8.5%. The goals of therapy are to prevent hypoglycemia in older patients at greatest risk of this adverse drug reaction. There is no rationale for reducing the carvedilol dose, and given her normal basic metabolic panel and blood pressure, reducing potassium chloride or discontinuing lisinopril is not indicated at this time (Answers B–D are incorrect).

7. Answer: D
Identifying reversible or underlying causes, such as pain or constipation, should be completed first when a patient experiences new behavioral changes. Given this patient's history of OA and advancing dementia, she may be unable to accurately communicate her pain. Changing acetaminophen from as needed to scheduled

should be the first intervention to rule out an underlying cause to this new behavior (Answer D is correct). The off-label use of atypical antipsychotic medications in patients with behavioral symptoms of dementia should be reserved for patients who pose a danger to themselves or others or experience hallucinations or delusions that are stressful to them (Answers A and B are incorrect). Currently, no evidence supports the use of pimavanserin in AD, and it should be reserved for patients with PD psychosis (Answer C is incorrect).

8. Answer: A

Any new symptom of UI in an older adult should be thoroughly evaluated to determine whether there is a reversible cause. Infection, or the "I" in the mnemonic DRIP, may be the cause of this patient's new symptoms. Urinalysis would be the most appropriate intervention for this reversible cause of incontinence (Answer A is correct). Mirabegron is reasonable for urge incontinence or overactive bladder once reversible causes have been ruled out (Answer C is incorrect). Duloxetine has been used off-label for stress incontinence (Answer D is incorrect). Pelvic floor muscle exercises or Kegel exercises should be first-line therapy for stress, urge, or mixed incontinence in women (Answer B is incorrect).

9. Answer: C

In this patient with comorbid conditions of hypertension and BPH, the choice of α-blockers is based on the adverse effect profiles. This patient has an elevated PVR volume, so changing tamsulosin to doxazosin might reduce both blood pressure and urinary retention; merely changing to another selective α-blocker might not provide adequate relief of both conditions (Answer C is correct; Answer A is incorrect). Increasing the atenolol dose would address only the increased blood pressure, without affecting the current problem of acute urinary retention (Answer B is incorrect). The patient is receiving moderate doses of a controlled-release opioid, so reducing the hydromorphone dose for breakthrough pain would unlikely help reduce the obstruction that may be worsened by the narcotics (Answer D is incorrect).

10. Answer: B

Because of continued elevated PVR volume with reported symptoms, combination therapy is recommended for this patient. Doxazosin plus finasteride is the most extensively studied (Answer B is correct). Tamsulosin plus dutasteride is also an extensively studied combination in BPH. Tadalafil use with doxazosin and other nonselective α_1-blockers is not recommended because of increased risk of hypotension (Answer A is incorrect). Alfuzosin is a selective α_1-blocker and should not be used in combination with other α_1-blockers (Answer C is incorrect). Currently, evidence is insufficient to support the efficacy of saw palmetto (Answer D is incorrect).

11. Answer: D

In patients with recurring RA symptoms, severe disease activity, and the presence of a poor prognostic factor (anti–cyclic citrullinated peptides), adding a biologic DMARD (e.g., infliximab) to optimized methotrexate therapy follows guidelines from the 2021 ACR recommendations update for the treatment of RA (Answer D is correct). Specifically, these guidelines recommend either double- or triple-combination DMARD therapy for patients with an inadequate response to methotrexate. Glucocorticoid therapy is no longer recommended as bridge therapy (Answer A is incorrect). Changing methotrexate from the oral route to the intramuscular route would offer no significant benefit in this case (Answer B is incorrect). Similarly, changing methotrexate to monotherapy with leflunomide would provide no significant benefit (Answer C is incorrect).

12. Answer: C

A different XOI (e.g., febuxostat) should be tried in the setting of intolerance or adverse effects before a uricosuric agent is tried (Answer C is correct). The allopurinol dose should not be increased at this time because of the presence of a new-onset rash. This may be an adverse effect associated with allopurinol; therefore, allopurinol should be discontinued (Answer A is incorrect). There is no acute need to restart NSAID therapy at this time because this patient's pain from the acute flare has resolved, and he is not currently experiencing an acute attack (Answer B is incorrect). Pegloticase is reserved for patients with a severe gout burden whose disease is refractory to or intolerant of other ULTs (Answer D is incorrect).

Pulmonary Disorders and Adult Immunizations

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Pulmonary Disorders and Adult Immunizations

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Learning Objectives

1. Design a patient-centered pharmacotherapy plan for initial treatment of asthma and chronic obstructive pulmonary disease according to evidence-based guidelines.
2. Assess the severity of a patient's asthma and chronic obstructive pulmonary disease on the basis of clinical presentation.
3. Adjust a patient's medication therapy for asthma and chronic obstructive pulmonary disease on the basis of symptom severity and clinical presentation.
4. Determine appropriate immunizations for an adult on the basis of patient-specific considerations, including age, medical conditions, contraindications, and immunization status.

Abbreviations in This Chapter

ACO	Asthma-COPD overlap
CAT	COPD Assessment Test
CCQ	COPD Control Questionnaire
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
DPI	Dry powder inhaler
ED	Emergency department
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Institute for Obstructive Lung Disease
HPV	Human papillomavirus
ICS	Inhaled corticosteroid
IL-5	Interleukin-5
LA	Long-acting
LABA	Long-acting β_2-agonist
LAMA	Long-acting anticholinergic/muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MDI	Metered-dose inhaler
MenACWY	Serogroups A, C, W, and Y meningococcal vaccine
MenB	Serogroup B meningococcal vaccine
mMRC	Modified Medical Research Council
OCS	Oral corticosteroid
PDE-4	Phosphodiesterase type 4
PEFR	Peak expiratory flow rate
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
SA	Short-acting
SABA	Short-acting β_2-agonist
SAMA	Short-acting anticholinergic/muscarinic antagonist
Sao_2	Oxygen saturation
Td	Tetanus and diphtheria vaccine
Tdap	Tetanus, diphtheria, and pertussis vaccine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.

A 20-year-old woman presents to the clinic with an asthma exacerbation. She states that she has been using her boyfriend's albuterol inhaler on a regular basis for the past 2 years. During the past few months, she has been using the inhaler on a daily basis and sometimes at night.

1. Which description best classifies her asthma severity?
   A. Mild intermittent.
   B. Mild persistent.
   C. Moderate persistent.
   D. Severe persistent.

2. Which is the best asthma maintenance therapy for this patient?
   A. Fluticasone low dose.
   B. Montelukast.
   C. Fluticasone low dose plus salmeterol.
   D. Fluticasone high dose.

3. Which type of data best classifies the number of times a low-dose inhaled corticosteroid/formoterol inhaler is used in 1 month?
   A. Nominal.
   B. Ordinal.
   C. Interval.
   D. Ratio.

4. You are designing a study in which you will compare the percentages of patients with an asthma-related hospitalization receiving fluticasone/salmeterol and those receiving fluticasone alone. Which statistical test is best for analyzing this comparison?
   A. Analysis of variance (ANOVA).
   B. Chi-square.
   C. Mann-Whitney *U* test.
   D. Unpaired t-test.

5. A 22-year-old woman with asthma is taking an albuterol metered-dose inhaler (MDI) 2 puffs as needed and fluticasone 110 mcg/puff MDI 2 puffs twice daily. She received the influenza vaccine during last year's influenza season, completed the mRNA coronavirus disease 2019 (COVID-19) vaccine series, and her last tetanus vaccine (tetanus, diphtheria, and pertussis [Tdap]) was at age 17; there is no documentation of her having received a pneumococcal vaccine. Which is the best vaccine for her to receive at her next family medicine clinic appointment, scheduled for July?
   A. Influenza.
   B. Pneumococcal.
   C. Tetanus and diphtheria (Td).
   D. Herpes zoster.

6. A 60-year-old man is diagnosed with chronic obstructive pulmonary disease (COPD) today. He reports experiencing symptoms most days of the week. His Modified Medical Research Council (mMRC) score is 1. His spirometry reveals a forced expiratory volume in 1 second (FEV_1) of 70% of predicted and an FEV_1/forced vital capacity (FEV_1/FVC) of 60% of predicted. He has had no previous COPD exacerbations. Which medication is best to initiate?
   A. Inhaled fluticasone.
   B. Inhaled tiotropium.
   C. Inhaled fluticasone/salmeterol.
   D. Oral roflumilast.

7. A 75-year-old woman with a 50 pack-year history of tobacco use presents to her primary care physician with a complaint of worsening shortness of breath over the past 6 months. She has no documented history of asthma or COPD. Which symptom is most consistent with the diagnosis of COPD?
   A. Dyspnea that is progressive, persistent, and worse with exertion.
   B. FEV_1/FVC greater than 70% of predicted.
   C. Chronic cough present only at night.
   D. COPD Assessment Test (CAT) score of 5.

8. A 68-year-old man was given a diagnosis of COPD 1 year ago, and his symptoms have been managed with an albuterol inhaler as needed and umeclidinium/vilanterol since. He reports adherence to current regimen with appropriate inhaler technique. Recent spirometry revealed an FEV_1/FVC less than 70% and FEV_1 of 65%. Last week, he was discharged from the hospital after his second COPD exacerbation in the past year. His current mMRC score is 1 and blood eosinophil count is 212 cells/mcL. Which maintenance therapy is most appropriate for this patient?
   A. Continue umeclidinium/vilanterol.
   B. Continue umeclidinium/vilanterol and add roflumilast.
   C. Continue umeclidinium/vilanterol and add fluticasone.
   D. Discontinue umeclidinium/vilanterol and start fluticasone furoate/umeclidinium/vilanterol.

9. A 32-year-old woman, 30 weeks pregnant, is seen for a routine prenatal check today (October). This is her second pregnancy in 3 years. During her first pregnancy, she received Tdap at 36 weeks' gestation; her last tetanus booster was at age 21. She received all of her routine childhood immunizations and is up to date with COVID-19 vaccines. Which immunizations would be best for her today?
   A. Td.
   B. Td and influenza.
   C. Tdap.
   D. Tdap and influenza.

10. A 21-year-old man is seen for his annual wellness exam in July. He received an influenza vaccine last October but states that it was his first immunization in about 10 years, besides completing the mRNA COVID-19 vaccine series. He works full-time at an office job that requires no travel. Which vaccines would be best for him today?

    A. Tdap, human papillomavirus (HPV).

    B. Tdap, influenza, meningococcal polysaccharide.

    C. Td, meningococcal polysaccharide, HPV.

    D. Td, influenza.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. Task 1.1: Knowledge statements: 1.1.1-1.1.6, 1.1.8, 1.1.10, 1.1.14-1.1.17
    b. Task 1.2: Knowledge statements: 1.2.1-1.2.4
    c. Task 1.3: Knowledge statements: 1.3.1-1.3.7
2. Application of Evidence to Practice and Education
    a. Task 2.2: Knowledge statements: 2.2.3, 2.2.4
3. Healthcare Systems and Population Health
    a. Task 3.1: Knowledge statements: 3.1.2
    b. Task 3.3: Knowledge statements: 3.3.1

I. ASTHMA

Guidelines:

Expert Panel Working Group of the NHLBI administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at https://www.nhlbi.nih.gov/health-topics-asthma-management-guidelines-2020-updates.

Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2022. Available at www.ginasthma.org/.

A. Definition: Asthma is a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, breathlessness, cough, and chest tightness, particularly at night or early in the morning. During episodes, there is variable airway obstruction, often reversible spontaneously or with treatment. There is also increased bronchial hyperresponsiveness to a variety of stimuli.

B. Diagnosis
   1. Episodic symptoms of airflow obstruction are present.
   2. Airway obstruction is reversible (FEV_1 improves by 12% or more after short-acting β_2-agonists [SABAs]). Table 1 provides additional information for interpretation of spirometry results.
   3. Alternative diagnoses are excluded.
   4. Asthma versus COPD:
      a. Cough is usually nonproductive with asthma and productive with COPD.
      b. FEV_1 is reversible with asthma but irreversible with COPD.
      c. Cough is worse at night and early in the morning with asthma; it occurs throughout the day with COPD.
      d. Asthma is often related to allergies and environmental triggers; patients with COPD have a common history of smoking or exposure to other irritants.
      e. Asthma can be reversible; lung damage from COPD is irreversible.
   5. Asthma-COPD overlap (ACO)
      a. No single definition of ACO is well defined or commonly accepted.
      b. ACO does not refer to a single disease state; rather, it is a clinical phenotype with shared clinical features of two separate diseases.
      c. Characterized by persistent airflow limitation and features associated with both asthma and COPD
      d. Table 2 includes clinical features of patients with asthma and/or COPD with recommended initial treatments.

Table 1. Interpreting Spirometry

Component	What It Measures	Normal Values
FEV_1	Volume of air exhaled forcefully in the first second of maximal expiration	Normal is ≥ 80% In asthma, reversibility is shown by an increase in FEV_1 ≥ 12% or FVC > 200 mL after SABA
FVC	Maximum volume of air that can be exhaled after full inspiration	Reported in liters and percentage predicted Adults with normal lung function can empty 80% of air in < 6 seconds
FEV_1/FVC ratio	Percentage of lung capacity able to be expelled in one second	Normal: Within 5% of predicted range, which varies with age; usually 75%–80% in adults Decreased in obstructive disease (asthma, COPD) (< 70%)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SABA = short-acting β_2-agonist.

Table 2. Initial Treatment Approach in Patients with Asthma and/or COPD

Adults with Chronic Respiratory Symptoms (dyspnea, cough, chest tightness, and wheeze)			
	Treat as asthma if several of the following features are present:	**Treat as asthma** if features of both asthma and COPD are present:	**Treat as COPD** if several of the following features are present:
History	– Symptoms vary over time and in intensity – Triggers: Laughing, exercise, allergens, seasonal – Onset < 40 yr of age – Symptoms improve with bronchodilators or ICS within days to weeks	– Symptoms intermittent or episodic – Age at onset varies – May have history of smoking and/or toxic exposures, low birth weight, or respiratory illness (e.g., tuberculosis) – Any asthma features listed in the column to the left (e.g., triggers, symptom improvement with bronchodilators or ICS, current asthma diagnosis or previous diagnosis as a child)	– Persistent dyspnea on most days – Onset > 40 yr of age – Limitation of physical activity – May have been preceded by cough or sputum – Bronchodilator provides limited relief – History of smoking and/or toxic exposures, low birth weight, or respiratory illness (e.g., tuberculosis) – No past/current asthma diagnosis
Lung function	– Variable expiratory airflow limitation – Persistent airflow limitation may be present	– Persistent expiratory airflow limitation – With or without bronchodilator reversibility	– Persistent expiratory airflow limitation – With or without bronchodilator reversibility
Initial treatment	– ICS-containing treatment essential – Do not give LABA and/or LAMA without ICS – Avoid maintenance OCS	– ICS-containing treatment essential – Additional COPD treatments per GOLD recommendations – Do not give LABA and/or LAMA without ICS – Avoid maintenance OCS	– Treat as COPD per GOLD recommendations – Avoid high-dose ICS, avoid maintenance OCS – Reliever containing ICS is not recommended
Reevaluate in 2–3 mo. Specialist referral if diagnosis remains uncertain or treatment response is inadequate			

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist; OCS = oral corticosteroid.

Information from: Global Initiative for Asthma (GINA). 2022 GINA Report. Global Strategy for Asthma Management and Prevention. Available at https://ginasthma.org/gina-reports/.

C. Classification of Asthma Severity and Control (Tables 3 and 4)
   1. GINA 2022 assessment of asthma in adults
      a. Assess symptom control from frequency of day- and nighttime symptoms, reliever inhaler use, and activity limitation.
      b. Consider symptom tools such as the Asthma Control Test and Asthma Control Questionnaire.
      c. Assess risk of future exacerbations, even when control is good.
   2. GINA 2022 assessment of asthma control in children 6–11 years old
      a. Symptom control on the basis of symptoms, limitation of activities (daily activities, sports, play, social life, school attendance), and use of rescue medication
      b. Parents may report irritability, tiredness, and mood changes when asthma is uncontrolled.
      c. Asthma control scores for children include Childhood Asthma Control Test, Asthma Control Questionnaire, and Test for Respiratory and Asthma Control in Kids.
   3. Categories of asthma severity
      a. Mild: Well controlled on step 1 or step 2 treatment
      b. Moderate: Well controlled on step 3 treatment
      c. Severe: Requires step 4 or step 5 treatment to prevent it from being "uncontrolled" or if it remains uncontrolled despite step 4 or 5 treatment

Table 3. Classification of Asthma Severity in Adults and Children According to NAEPP EPR3[a]

Components	Age Group (yr)	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Frequency of symptoms	All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Throughout the day
Nighttime awakening	≥ 12	≤ 2 times/mo	3 or 4 times/mo	More than once weekly but not nightly	Often 7 times/wk
	5–11				
	0–4	0	1 or 2 times/mo	3 or 4 times/mo	More than once weekly
SABA; used for symptom control	All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Several times a day
Interference with normal activity	All ages	None	Minor limitation	Some limitations	Extremely limited
FEV_1/FVC[b]	≥ 12	Normal	Normal	Reduced 5%	Reduced > 5%
	5–11	> 85%	> 80%	75%–80%	< 75%
	0–4	N/A			
FEV_1 (% of normal)	≥ 12	> 80% (normal)	> 80% (normal)	> 60% to < 80%	< 60%
	5–11				
	0–4	N/A			
Exacerbations requiring oral steroids	≥ 12	0 or 1/yr	≥2/yr[c]		
	5–11				
	0–4	0 or 1/yr	≥2 in 6 mo or ≥4 wheezing episodes lasting > 1 day per year[d]		

Table 3. Classification of Asthma Severity in Adults and Children According to NAEPP EPR3[a] *(Cont'd)*

Components	Age Group (yr)	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Recommended step for initiating treatment (see Table 5)	≥ 12	Step 1	Step 2	Step 3[e] and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	5–11				Step 3[d] or 4 and consider short course of oral steroids
	0–4				Step 3 and consider short course of oral steroids

[a]The patient is classified according to the sign or symptom that is in the most severe category.

[b]Normal FEV_1/FVC: 8–19 yr old, 85%; 20–39 yr old, 80%; 40–59 yr old, 75%; 60–80 yr old, 70%.

[c]Considered the same as in patients who have persistent asthma, even without impairment levels consistent with persistent asthma.

[d]Episodes lasting > 1 day and risk factors for persistent asthma.

[e]For ages 5–11, initial step 3 therapy should be medium-dose ICS.

EPR = Expert Panel Report; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; National Asthma Education and Prevention Program (NAEPP); SABA = short-acting β_2-agonist. N/A = not applicable.

Adapted from: NIH Asthma Guidelines. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. Available at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma.

Table 4. Assessing Asthma Control in Adults and Children ≥ 6 Yr

In the past 4 wk, has the patient had:			Well Controlled	Partly Controlled	Uncontrolled
Daytime asthma symptoms more than twice/week?	Yes	No	None of these	1 or 2 of these	3 or 4 of these
Any night waking because of asthma?	Yes	No			
SABA needed for symptoms more than twice/week?	Yes	No			
Any activity limitation because of asthma?	Yes	No			

SABA = short-acting β_2-agonist.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2022. Available at www.ginasthma.org/.

D. Treatment Goals
   1. Minimal or no chronic symptoms day or night
   2. Minimal or no exacerbations
   3. No limitations on activities, no school or work missed
   4. Maintenance of (near) normal pulmonary function
   5. Minimal use of reliever medications
   6. Minimal or no adverse effects from medications

E. Risk Factors for Poor Outcomes
   1. Uncontrolled asthma symptoms
   2. Medication factors: No inhaled corticosteroid (ICS), poor adherence, incorrect inhaler technique, short-acting β_2-agonist (SABA) use greater than 1 x 200 dose canister/month
   3. Comorbid conditions: Obesity, gastroesophageal reflux disease, anxiety, depression, pregnancy
   4. Environmental exposure: Smoking, allergens, air pollution
   5. Lung function: FEV_1 less than 60% predicted, higher degree of reversibility
   6. Fractional exhaled nitric oxide (FeNO) in allergic adults taking ICSs

F. Treatment Guidelines (Table 5)

Table 5. Stepwise Approach for Management of Asthma in Individuals Age 12 Years and Older

Guideline		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6[c]
NAEPP 2020 Focused Update	**Controller**	SABA PRN	Low-dose ICS or concomitant low-dose ICS and SABA PRN[a] Alternative: LTRA or cromolyn or theophylline[b]	Low-dose ICS-formoterol[a] Alternative: Medium-dose ICS or low-dose ICS-LABA or low-dose ICS + LAMA[a] or LTRA[b] or low-dose ICS + theophylline or zileuton[b]	Medium-dose ICS-formoterol[a] Alternative: Medium-dose ICS-LABA or medium-dose ICS + LAMA[a] or medium-dose ICS + LTRA, theophylline, or zileuton[b]	Medium/ highdose ICS-LABA + LAMA[a] Alternative: Medium/high dose ICS-LABA or high-dose ICS + LTRA[b]	High-dose ICS-LABA + OCS
	Reliever	SABA PRN	Low-dose ICS and SABA PRN[a] Alternative: SABA PRN	Low-dose ICS-formoterol PRN[a] Alternative: SABA PRN	Medium-dose ICS-formoterol PRN[a] Alternative: SABA PRN	SABA PRN	SABA PRN
			Conditionally recommend adjunct subcutaneous immunotherapy in patients with controlled asthma			Consider adding asthma biologics	
GINA	**Track 1: Preferred; especially if likely to be poorly adherent with daily ICS-containing controller therapy**						
	Controller	Low dose ICS-formoterol PRN		Low-dose ICS-formoterol	Medium-dose ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± asthma biologics Consider high-dose ICS-formoterol	
	Reliever	Low dose ICS-formoterol PRN					
	Track 2: Assess likelihood of adherence						
	Controller	Take ICS whenever SABA taken	Low-dose ICS	Low-dose ICS-LABA	Medium/high dose ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± asthma biologics Consider high-dose ICS-LABA	
	Reliever	SABA PRN					
	Alternative controllers for either track						
			Low dose ICS whenever SABA taken, or daily LTRA or HDM SLIT	Medium-dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS	Add azithromycin (adults) or LTRA; add low dose OCS	

GINA = Global Initiative for Asthma; HDM = house dust mite; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; National Asthma Education and Prevention Program (NAEPP); OCS = oral corticosteroid; PRN = as needed; RTI = respiratory tract infection; SABA = short-acting β_2-agonist; SLIT = sublingual immunotherapy.

[a]Updates based on the 2020 guidelines.

[b]Cromolyn, LTRAs, and theophylline were not considered in 2020 update and/or have limited availability in the United States, and/or have increased risk of adverse drug reactions and need for monitoring making use less desirable.

[c]Data on the use of LAMA therapy in Step 6 was not reviewed; therefore, no recommendation was made.

Information from: 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Available at www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates; Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2022. Available at www.ginasthma.org/.

G. Pharmacologic Therapy for Asthma (Tables 6 and 7)

Table 6. Pharmacologic Agents Used for Asthma and COPD

Generic	Brand	Dose	Adverse Effects	Comments
ICSs				
Beclomethasone MDI 40 mcg/puff 80 mcg/puff	QVAR RediHaler (breath activated)	See ICS dosing table	Oral candidiasis Hoarseness May slow bone growth in children but similar adult height	ICSs are first line for persistent asthma Use holding chambers only if needed for technique; not needed or well studied with HFA inhalers; holding chambers are only for MDIs, cannot be used for DPIs; holding chamber with a mask can be used for young children Per GINA guideline update rinsing of mouth not required Onset of improvement is 5–7 days; additional benefit may occur over several weeks Pulmicort Respules are the only nebulized steroid available Arnuity Ellipta inhalation powder is contraindicated in severe hypersensitivity to milk proteins
Budesonide DPI 90 mcg/puff 180 mcg/puff Budesonide inhalation solution 0.25-mg/2 mL 0.5-mg/2 mL 1-mg/2-mL	Pulmicort Flexhaler Pulmicort Respules			
Ciclesonide MDI 80 mcg/puff 160 mcg/puff	Alvesco HFA			
Fluticasone propionate MDI 44 mcg/puff 110 mcg/puff 220 mcg/puff Fluticasone propionate DPI 50 mcg/puff 100 mcg/puff 250 mcg/puff Fluticasone furoate DPI 50 mcg/puff 100 mcg/puff 200 mcg/puff Fluticasone propionate DPI 55 mcg/puff 113 mcg/puff 232 mcg/puff	Flovent HFA Flovent Diskus Arnuity Ellipta 1 inhalation once daily ArmonAir Digihaler			
Mometasone DPI 110 mcg/puff 220 mcg/puff Mometasone MDI 50 mcg/puff 100 mcg/puff 200 mcg/puff	Asmanex Twisthaler Can be used once daily Asmanex HFA			
SAMAs				
Ipratropium MDI 17 mcg/puff Ipratropium inhalation solution 0.5 mg/2.5 mL	Atrovent HFA	2 puffs QID (up to 12 puffs/24 hr) 0.5 mg every 6–8 hr	Headache Flushed skin Blurred vision Tachycardia Palpitations	Used mainly for COPD and for acute asthma exacerbations necessitating emergency treatment

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LAMAs				
Aclidinium bromide DPI 400 mcg/puff	Tudorza Pressair	1 puff BID	Headache Flushed skin Blurred vision Tachycardia Palpitations Acute urinary retention Cough (Respimat device)	LAMA for COPD
Glycopyrrolate inhalation solution 25 mcg/vial	Lonhala Magnair	Inhale one vial (25 mcg) twice daily		LAMA approved for COPD Only used with PARI nebulizer
Revefenacin inhalation solution 175 mcg/vial	Yupelri	Inhale 1 vial (175 mcg) once daily	Cough, nasopharyngitis, URTI, headache, back pain	Once-daily nebulized LAMA; for use with standard jet nebulizer
Tiotropium DPI 18 mcg/capsule Tiotropium inhalation spray 1.25 mcg/spray (asthma) 2.5 mcg/spray (COPD)	Spiriva HandiHaler Spiriva Respimat	Inhale contents of 1 capsule/day 2 puffs once daily		Spiriva Respimat is the only LAMA indicated for long-term maintenance treatment of asthma for those ≥ 12
Umeclidinium DPI 62.5 mcg/blister	Incruse Ellipta	1 inhalation once daily		Once-daily LAMA for COPD
SABAs				
Albuterol MDI 90 mcg/spray Albuterol inhalation solution 0.63 mg/3 mL 2.5 mg/3 mL 2.5 mg/0.5 mL	Proventil HFA Ventolin HFA ProAir HFA ProAir RespiClick DPI ProAir Digihaler DPI	2 puffs every 4–6 hr PRN 2.5 mg three or four times daily PRN	Tremor Tachycardia (less with levalbuterol) Hypokalemia Hypomagnesemia Hyperglycemia Tachyphylaxis *R*-enantiomer of albuterol Duration (MDI): 3–4 hr (<6)	Used for acute bronchospasm; regular use indicates poor control Duration of effect (MDI): 3–4 hr (< 6)
Levalbuterol MDI 45 mcg/spray Levalbuterol inhalation solution 0.63 mg/3 mL; also available in 0.31 mg/3 mL, 1.2 mg/3 mL, and 1.25 mg/0.5 mL	Xopenex, generic	2 puffs every 4–6 hr PRN 0.63 mg TID every 6–8 hr Maximum: 1.25 mg TID		

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LABAs				
Arformoterol inhalation solution 15 mcg/2 mL	Brovana	Inhale 1 vial BID		Arformoterol is the *R,R*-isomer of racemic formoterol
Formoterol inhalation solution 20 mcg/2 mL	Perforomist	Inhale 1 vial BID		Onset of action 1–3 min but should not be used as acute therapy Should not be used as monotherapy for asthma
Olodaterol inhalation spray 2.5 mcg/spray	Striverdi Respimat	2 puffs once daily		Indicated only for COPD Duration of action: 24 hr
Salmeterol DPI 50 mcg/puff	Serevent Diskus	Inhale 1 blister/puff BID		Not for acute symptoms Should not be used as monotherapy for asthma Duration: 8–12 hr
Combination SABA/SAMA				
Albuterol/ipratropium 100 mcg/20 mcg/puff	Combivent Respimat	1 puff QID Maximum dose 6 puffs/day	Cough Dyspnea HA Bronchitis Nasopharyngitis URTI	Used primarily for COPD
Ipratropium/albuterol inhalation solution 0.5 mg–3 mg/3 mL	Generic	1 vial every 4–6 hr		
Combination LAMA/LABA				
Aclidinium/formoterol DPI 400 mcg/12 mcg	Duaklir Pressair	1 inhalation BID	URTIs, headache, back pain	Used for maintenance of COPD
Glycopyrrolate/formoterol fumarate DPI 9 mcg/4.8 mcg/spray	Bevespi Aerosphere	2 inhalations BID	Urinary tract infections Cough	
Tiotropium/olodaterol inhalation spray 2.5 mcg/2.5 mcg/spray	Stiolto Respimat	2 inhalations once daily		
Umeclidinium/vilanterol DPI 62.5 mcg/25 mcg/puff	Anoro Ellipta	1 inhalation once daily		

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
Combination ICS/LABA				
Budesonide/formoterol MDI 80 mcg/4.5 mcg/puff 160 mcg/4.5 mcg/puff	Symbicort (generic available)	2 puffs BID	Nasopharyngitis HA URTI Sinusitis Oral candidiasis Vomiting Influenza Back pain	Single maintenance and reliever therapy (SMART) for asthma: 5–11 years: 1–2 puffs as needed up to a total daily maintenance and reliever dose of 8 puffs (36 mcg) 12 years and older: 1–2 puffs as needed up to a total daily maintenance and reliever dose of 12 puffs (54 mcg)
Fluticasone/salmeterol DPI 100 mcg/50 mcg/puff 250 mcg/50 mcg/puff 500 mcg/50 mcg/puff	Advair Diskus Wixela Inhub (generic available)	1 puff BID	URTI Pharyngitis Dysphonia Oral candidiasis Cough HA N/V	
Fluticasone/salmeterol MDI 45 mcg/21 mcg/puff 115 mcg/21 mcg/puff 230 mcg/21 mcg/puff	Advair HFA	2 puffs BID	URTI Throat irritation Dysphonia HA Dizziness N/V	
Fluticasone propionate/salmeterol DPI 55 mcg/14 mcg/puff 113 mcg/14 mcg/puff 232 mcg/14 mcg/puff	AirDuo RespiClick AirDuo Digihaler	One inhalation twice daily	Nasopharyngitis Oral candidiasis Back pain HA Cough	Not FDA-approved for COPD Generic equivalent of AirDuo is available
Fluticasone furoate/vilanterol DPI 100 mcg/25 mcg 200 mcg/25 mcg	Breo Ellipta	1 inhalation once daily	Nasopharyngitis URTI HA Oral candidiasis Back pain Influenza Dysphonia Cough Pharyngitis	
Mometasone/formoterol DPI 100 mcg/5 mcg/puff 200 mcg/5 mcg/puff	Dulera	2 puffs BID	Nasopharyngitis Sinusitis HA	Not FDA-approved for COPD
Combination ICS/LAMA/LABA				
Fluticasone furoate/umeclidinium/vilanterol DPI 100 mcg/62.5 mcg/25 mcg/blister	Trelegy Ellipta	One inhalation once daily	URTI Pneumonia Bronchitis Oral candidiasis HA Back pain Arthralgia Influenza Sinusitis	
Budesonide/glycopyrrolate/formoterol MDI 160 mcg/9 mcg/4.8 mcg/puff	Breztri Aerosphere	2 puffs BID	URTI Pneumonia Back pain Oral candidiasis Influenza Muscle spasm Cough Sinusitis	

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LTRAs				
Montelukast Oral 10-mg tablet Chewable 4- and 5-mg tablets Oral granules 4 mg/packet	Singulair	Dose in the evening Adults and those ≥ 15 yr: 10 mg/day Children 6 to < 15 yr: 5 mg/day Children 1 to < 6 yr: 4 mg/day	Headache GI upset Hepatotoxicity (zafirlukast and zileuton only) Zafirlukast: Monitor symptoms, may consider regular LFT monitoring but not needed Zileuton: Monitor LFTs (baseline, every month × 3 mo, every 2–3 mo for remainder of first year)	Also indicated in exercise-induced bronchospasm and seasonal and perennial allergic rhinitis FDA approved for use in children ≥ 1 yr; used in children ≥ 6 mo Churg-Strauss syndrome associated with tapering doses of steroids *In March 2020, FDA added a boxed warning for montelukast because of the risk of serious neuropsychiatric events
Zafirlukast 10-mg tablet 20-mg tablet	Accolate	10–20 mg BID		Drug interactions: Warfarin, erythromycin, theophylline FDA approved for children ≥ 5 yr Bioavailability decreases with food; take 1 hr before or 2 hr after meals
Zileuton 600-mg ER tablet	Zyflo	1200 mg BID		Drug interactions: warfarin, theophylline Only for those ≥ 12 yr Less desirable for asthma treatment due to limited studies as adjunctive therapy and the need to monitor liver function
Monoclonal antibody/IgE–binding inhibitor				
Omalizumab	Xolair	150–375 mg SC every 2–4 wk Dose and frequency based on baseline IgE and weight in kilograms Do not inject > 150 mg per injection site	Injection site reactions: Urticaria Thrombocytopenia (transient) Anaphylaxis (rare) Malignancy	September 2014: FDA Drug Safety Communication. Slightly increased risk of cardiovascular and cerebrovascular serious adverse events, including MI, unstable angina, TIA, PE/DVT, pulmonary HTN; no increased risk of stroke or CV death Used in severe persistent allergy-related asthma Use in those ≥ 12 yr Half-life: 26 days Second-line therapy Expensive No longer required to be only administered in a healthcare setting Prefilled syringe available for home use

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
IL-4 antagonist				
Dupilumab	Dupixent	400 mg SC x 1; then 200 mg SC every other week OR 600 mg SC x 1; then 300 mg SC every other week (use higher dose if concomitant OCS required)	Hypersensitivity reaction Conjunctivitis and keratitis Injection site reactions Oropharyngeal pain Eosinophilia	Use in those ≥ 12 yr Indicated as add-on in those with eosinophilic asthma or who are OCS-dependent Avoid use of live vaccines
IL-5 antagonist				
Mepolizumab	Nucala	100 mg SC every 4 wk in the upper arm, thigh, or abdomen (≥ 12 yr) 40 mg SC every 4 wk (6–11 yr)	Injection-site reactions: Headache Fatigue Herpes zoster infection Hypersensitivity reaction (rare)	FDA-approved November 2015 Add-on maintenance therapy in severe asthma in ages ≥ 6 with an eosinophilic phenotype No eosinophil threshold is listed. However, data suggest that the absolute blood eosinophil count should be ≥ 150/mm^3 if patient is not taking daily systemic corticosteroids Reduces rate of asthma exacerbations by > 50%; reduces corticosteroid dose by 50%
Reslizumab	Cinqair	3 mg/kg IV infusion over 20–50 min every 4 wk	Increased creatine kinase concentration Myalgia Throat pain Anaphylaxis (rare)	FDA approval in March 2016 Add-on maintenance therapy in severe asthma in those ≥ 18 with an eosinophilic phenotype In clinical trials, the eosinophilic phenotype was defined as a peripheral blood absolute eosinophil count of ≥ 400/mm^3 if patient not taking daily systemic corticosteroids Reduces rate of asthma exacerbations by about 50% in these patients
Benralizumab	Fasenra	30 mg SC every 4 wk for the first 3 doses, followed by once every 8 wk in upper arm, thigh, or abdomen	Headache Pharyngitis Fever Hypersensitivity reaction	FDA-approved November 2017 Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
TSLP blocker				
Tezepelumab	Tezspire	210 mg SC every 4 wk	Pharyngitis Arthralgia Back pain	FDA approval in 2021 Add-on maintenance treatment of patients with severe asthma age 12 years and older Improved response is strongly correlated with higher blood eosinophil counts and FeNO levels

BID = twice daily; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DPI = dry powder inhaler; DVT = deep venous thrombosis; ER = extended release; FDA = U.S. Food and Drug Administration; FeNO = fractional exhaled nitric oxide; GI = gastrointestinal; GINA = Global Initiative for Asthma; HA = headache; HFA = hydrofluoroalkane; HTN = hypertension; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IV = intravenous(ly); LAMA = long-acting anticholinergic/muscarinic antagonist; LFT = liver function test; MDI = metered dose inhaler; MI = myocardial infarction; N/V = nausea and vomiting; PE = pulmonary embolism; PRN = as needed; QID = four times daily; SABA = short-acting β_2-agonist. SAMA = short-acting anticholinergic/muscarinic antagonist; SC = subcutaneously; TIA = transient ischemic attack; TID = three times daily; TSLP = thymic stromal lymphopoietin; URTI = upper respiratory tract infection.

Table 7. Inhaled Corticosteroid Daily Dosing in Children and Adults

Inhaled Corticosteroids: Available Products and Strengths (mcg unless noted)	Low-Dose (mcg/day)			Medium-Dose (mcg/day)			High-Dose (mcg/day)		
Age group (yr)	0–5	6–11	≥ 12	0–5	6–11	≥ 12	0–5	6–11	≥ 12
Beclomethasone QVAR HFA 40, 80	50 (age 5 only)	50–100	100–200	200 (age 5 only)	> 100–200	> 200–400	N/A	> 200	> 400
Budesonide Pulmicort DPI 90, 180	N/A	100–200	200–400	N/A	> 200–400	> 400–800	N/A	> 400	> 800
Budesonide suspension for nebulization Pulmicort Respules 250, 500, 1000	500	250–500	N/A	1000	> 500–1000	N/A	N/A	> 1000	N/A
Ciclesonide[a,b] Alvesco HFA 80, 160	N/A	80	80–160	N/A	> 80–160	> 160–320	> 160–320	> 160	> 320
Fluticasone propionate Flovent HFA 50, 125, 250	50 (age ≥ 4)	50–100	100–250	100 (age ≥ 4)	> 100–200	> 250–500	N/A	> 200	> 500
Flovent DPI 50, 100, 250	N/A	50–100	100–250	N/A	> 100–200	> 250–500	N/A	> 200	> 500
Fluticasone furoate Arnuity Ellipta 50, 100, 200[a,c]	N/A	50	100	N/A	N/A	N/A	N/A	N/A	200
Mometasone Asmanex Twisthaler DPI 110, 220	110 (age ≥ 4)	110	110–220	220 (age ≥ 4)	> 220 – < 440	> 220–440	N/A	> 440	> 440
Asmanex HFA 50, 100, 200	100 (age 5 only)	100	200–400	N/A	N/A	N/A	N/A	200	> 400

[a]Doses are estimated from package insert.

[b]Ciclesonide was not available when the National Asthma Education and Prevention Program guidelines were published. The dose ranges are estimated from the package insert.

[c]Once daily.

DPI = dry powder inhaler; HFA = hydrofluoroalkane; N/A = not available.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2022. Available at www.ginasthma.org/.

Patient Cases

Questions 1–3 pertain to the following case.

A 23-year-old woman has been coughing and wheezing about twice weekly, and she wakes up at night about three times per month. She has never been given a diagnosis of asthma and has not been to a physician, she says, "in years." She uses her roommate's albuterol inhaler, but having recently run out of refills, she is seeking care. Her activities are not limited by her symptoms. Spirometry today reveals FEV_1 82% of predicted.

1. According to the NAEPP guidelines, which is the best classification of her asthma?
   A. Intermittent.
   B. Mild persistent.
   C. Moderate persistent.
   D. Severe persistent.

2. According to GINA guidelines, which medication is best to recommend for her, in addition to budesonide/formoterol MDI every 4–6 hours as needed?
   A. No additional therapy needed.
   B. Oral montelukast 10 mg/day.
   C. Mometasone DPI 220 mcg/puff 2 puffs daily.
   D. Budesonide/formoterol MDI 80/4.5 mcg per puff 2 puffs twice daily.

3. At first, the patient's symptoms were well controlled on your recommended therapy. However, when winter arrived, her symptoms were no longer well controlled, and she started using her budesonide/formoterol MDI 3 or 4 days per week during the day. Which is the preferred treatment change?
   A. No change in therapy is needed.
   B. Add budesonide/formoterol MDI 80/4.5 mcg per puff 2 puffs twice daily.
   C. Add montelukast orally 10 mg daily.
   D. Add mometasone DPI to 220 mcg/puff 2 puffs daily.

H. Types of Inhalation Devices (Table 8)

Table 8. Different Types of Inhalation Devices

Type and Name[a]	Specifics	Type of Inhalation	Shake or Prime	Dose Counter	Advantages and Limitations
MDIs					
HFA inhalers: ProAir, Ventolin, Proventil, Xopenex, Flovent, Alvesco, Asmanex HFA, Symbicort, Dulera, Advair HFA, Atrovent, Aerosphere (Bevespi, Breztri) Breath Actuated (QVAR RediHaler)	Drug is mixed with a propellant	Press down canister at the start of a slow, deep inhalation	Prime: Yes Shake: Yes	Yes, except Proventil, Xopenex, Alvesco	Benefits: Slow, deep breath is easier than forceful, quick breath; may be used with a spacer or holding chamber Limitation: Requires coordination; many people have difficulty with technique

Table 8. Different Types of Inhalation Devices *(Cont'd)*

Type and Name[a]	Specifics	Type of Inhalation	Shake or Prime	Dose Counter	Advantages and Limitations
Single Dose System DPIs					
HandiHaler (Spiriva) Neohaler (Arcapta, Utibron, Seebri)	Individual gelatin capsules containing drug must be inserted and pierced before each use and removed after each use	Inhalation should be a steady and deep breath, enough to hear the whirring sound of the capsule rattling. Inhalation does not need to be as forceful as with some DPIs. May take a second inhalation if powder remains in the capsule	Prime: No Shake: No	No But not needed	Benefit: Inhalation is easier because it does not have to be forceful Limitation: Need to load and pierce each capsule before use
Preloaded Multidose DPIs					
Pressair (Tudorza, Duaklir) Twisthaler (Asmanex) Flexhaler (Pulmicort) Diskus (Advair, Flovent, Serevent)	Multiple doses are included in each device, either as a reservoir or a multiunit dose; each device lasts about 1 mo	Inhalation is quick, forceful, and deep; deeper and more forceful than in single-dose systems	Prime: No, except Flexhaler Shake: No	Yes	Benefit: No need to load capsules before each inhalation Limitation: Inhalation is more difficult to do correctly because it must be quick and forceful
Ellipta (Anoro, Breo, Arnuity, Incruse)	Different multidose system; 2 separate blister strips that dispense inhalation powder Contraindicated in severe hypersensitivity to milk protein	Inhalation is deep and slow, not fast and forceful as with other DPIs	Prime: No Shake: No	Yes	Benefits: Easier inhalation than with other DPIs; no need to load capsules before each inhalation; once-daily dosing with only 1 inhalation each time, all medications that come in the Ellipta device are 1 inhalation once daily
Breath-Actuated DPI					
Respiclick (ProAir) Digihaler (ProAir, AirDuo, AromonAir)	Medication is automatically released on inhalation; canister is not pressed Digihaler is the first digital inhaler with built-in sensors that measure inspiratory flow and detect inhaler use when the cap is opened or the patient inhales. Information is sent wirelessly to the companion mobile app using Bluetooth technology	Deep breath; quickly and deeply with enough force for the medication to be released Cannot be used with a spacer or holding chamber Contraindicated in severe hypersensitivity to milk proteins	Prime: No Shake: No	Yes	Benefit: No need to coordinate breath with actuation as with all other albuterol devices (MDIs)

Table 8. Different Types of Inhalation Devices *(Cont'd)*

Type and Name[a]	Specifics	Type of Inhalation	Shake or Prime	Dose Counter	Advantages and Limitations
Soft Mist Inhaler					
Respimat (Combivent, Spiriva, Striverdi, Stiolto)	Dose of drug is in solution and is released through a nozzle with jets of mist Lung deposition and amount of drug delivered are independent of the patient's effort	Inhalation is slow and deep	Prime: Yes Each new inhaler needs to be assembled, readied, and primed before first use; this is somewhat complicated If not used in 3 days, prime with 1 inhalation released into air Full repriming needed if not used in 21 days. Shake: No	Yes	Benefits: Ease of inhalation, consistent drug delivery Limitation: Complicated steps to ready and prime inhaler each month and after not using for 21 days

[a]For generic names and drug class, see Table 6.

DPI = dry powder inhaler; HFA = hydrofluoroalkane.

I. Adjusting Asthma Treatment
   1. Control-based asthma management:
      a. Continuous cycle of treatment adjustment that involves assessment, treatment, and review
         i. Assess: Confirm diagnosis, symptom control and modifiable risk factors, comorbidities, inhaler technique, patient goals
         ii. Adjust: Treatment of modifiable risk factors and comorbidities, nonpharmacologic strategies, education and skills training, asthma medications
         iii. Review response: Symptoms, exacerbations, adverse effects, lung function, patient satisfaction
      b. Change in treatment on the basis of features of poor symptom control with or without other risk factors
      c. Accounts for both symptom control and future risk when choosing an asthma treatment
      d. Recommended approach to monitoring and adjusting treatment
      e. Alternative strategies for adjusting treatment
         i. In adults, leads to reduced exacerbations and similar levels of symptom control
         ii. Limited availability of routine sputum analysis
         iii. Recommended for adults with moderate or severe asthma who are in treatment centers that have experience with this technique
   2. FeNO
      a. In children/young adults, has been associated with reduced exacerbations
      b. In nonsmoking adults, no significant reduction in exacerbations
      c. Further study needed to identify populations most likely to benefit from FeNO-guided treatment

J. Single Maintenance and Reliever Therapy (SMART)
   1. Also called Maintenance and Reliever Therapy (MART) in GINA guidelines
   2. SMART therapy with ICS-formoterol reliever reduces severe exacerbation risk compared with regimens including a SABA reliever

K. Use of Long-Acting Antimuscarinic Antagonists (LAMAs) for Asthma
   1. Tiotropium Respimat is the only LAMA indicated for long-term treatment of asthma.
   2. Tiotropium is approved as add-on therapy in patients with asthma age 6 years and older.
   3. Recommended as an alternative add-on in step 4 because of insufficient evidence compared with ICS plus long-acting β_2-agonist (LABA)
   4. A preferred add-on in step 5
   5. Evidence shows improved lung function and increased time to severe exacerbation.

L. Pharmacologic Treatment of Patients with Clinical Features of Asthma and COPD
   1. If there are more features of asthma, use the treatment strategy for asthma.
   2. If there are more features of COPD, use the treatment strategy for COPD.
   3. If the clinical presentation includes features of both asthma and COPD, start with a low- or moderate-dose ICS and usually add a LABA or LAMA (www.ginasthma.org).

M. Long-Acting β_2-Agonists (FDA Drug Safety Communication 2010):
   1. Use of a LABA alone without a long-term asthma control drug such as an ICS is contraindicated because of an increased risk of severe worsening of asthma symptoms, leading to hospitalization and death in some children and adults.
   2. LABAs should not be used in patients whose asthma is adequately controlled by low- or medium-dose ICSs.
   3. LABAs should be used only as additional therapy for patients who are currently taking, but whose asthma is not adequately controlled by, a long-term asthma control agent (e.g., an ICS). An FDA review found no significant increase in risk of serious asthma outcomes with LABA use in combination with ICS (FDA Drug Safety Communication 2017)
   4. Once asthma control is achieved and maintained, patients should be assessed at regular intervals and stepped down (e.g., LABAs discontinued), if possible, and the patients should continue to be treated with a long-term asthma control agent (e.g., an ICS).
   5. Pediatric and adolescent patients who need a LABA and an ICS should use a combination product to ensure adherence to both medications.

N. Exercise-Induced Bronchospasm: Diagnosis, Prevention, and Treatment of Symptoms
   1. History of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise are suggestive of exercise-induced bronchospasm.
   2. Diagnosis is made with an exercise challenge in which a 15% decrease in FEV_1 or peak expiratory flow occurs before and after exercise, measured at 5-minute intervals for 20–30 minutes.
   3. Long-term control therapy, if otherwise appropriate (initiate or step-up), should be used, particularly if exercise-induced bronchospasm is frequent or severe.
   4. Pretreatment with SABA or low-dose ICS-formoterol and as needed for symptom relief is recommended.
   5. Leukotriene receptor antagonists (LTRAs) can attenuate symptoms in 50% of patients, but onset is hours after administration.

O. Monitoring
   1. Peak flow monitoring
      a. Symptom-based and peak flow–based monitoring have similar benefits; either is appropriate for most patients. Symptom-based monitoring is more convenient.
      b. Daily home peak flow monitoring may be considered for moderate to severe persistent asthma if the patient has a history of severe exacerbations or has poor perception of worsening of asthma symptoms.

c. Personal best peak expiratory flow rate (PEFR), not predicted PEFR, should be determined if a peak flow–based asthma action plan is being used.
    i. Personal best PEFR is the highest number attained after daily monitoring for 2 weeks twice daily when asthma is under good control.
    ii. Predicted PEFR is based on population norms for sex, height, and age.

2. Spirometry (only used in patients 5 years and older)
    a. At initial assessment
    b. After treatment is started and symptoms are stabilized (3–6 months)
    c. If prolonged or progressive loss of asthma control
    d. At least every 2 years or more often, depending on response to therapy

P. Asthma Action Plan (Table 9)
1. Usually symptom based (equal benefits of symptom-based and peak flow–based monitoring)
2. Permits home treatment of an asthma exacerbation
3. For all patients with early/mild symptoms:
    a. Increase reliever
    b. Provide early increase in controller
    c. Review response
4. For late/severe symptoms if peak expiratory flow or FEV_1 less than 60% best, or symptoms not improving after 48 hours:
    a. Continue reliever
    b. Continue controller
    c. Add prednisone 40–50 mg/day
    d. Contact physician
5. After initial treatment, immediate medical attention is needed if patient is at high risk of a fatal attack. Risk factors: asthma-related (history of severe attack [previous intubation or intensive care unit admission for asthma], ≥ 2 hospitalizations for asthma in past year, ≥ 3 ED visits for asthma in the past year, hospitalization or ED visit for asthma in the past month, using > 2 canisters of SABA a month, difficulty perceiving asthma symptoms), social (low socioeconomic status or inner-city residence, illicit drug use, major psychosocial problems), and comorbidities (cardiovascular disease, other chronic lung disease, chronic psychiatric disease).

Table 9. Asthma Action Plan

Zone	Signs and Symptoms	Treatment
Green	Doing well; no or minimal symptoms of coughing, wheezing, or dyspnea PEFR 80%–100% of personal best	Take long-term asthma control agent only (if one is prescribed) Use reliever inhaler 5–15 min before exercise if exercise-induced asthma and before known triggers Avoid things that make asthma worse
Yellow	Getting worse; increased frequency of symptoms (e.g., coughing, wheezing, chest tightness, or dyspnea); nighttime awakenings; decreased ability to engage in normal activities PEFR 50%–79% of personal best	Increase usual reliever (low-dose ICS-formoterol; increase frequency to max of 72 mcg formoterol/day; SABA: 2–4 puffs by MDI or 1 nebulizer treatment and repeat in 20 min, if needed). If complete response at 1 hr, contact clinician for follow-up instructions and consider OCS burst[a] If incomplete response in 1 hr (still some coughing, wheezing, or dyspnea), repeat SABA and add OCS burst; contact clinician that day for further instructions If poor response in 1 hr (e.g., marked coughing, wheezing, or dyspnea), repeat SABA immediately; add OCS burst; contact clinician immediately; proceed to the ED if the distress is severe and unresponsive to treatment; consider calling 911 May continue to use SABA every 3–4 hr regularly for 24–48 hr
Red	Medical alert (e.g., marked coughing, wheezing, or dyspnea); inability to speak more than short phrases; use of accessory respiratory muscles; drowsiness PEFR < 50% of personal best	Begin treatment and consult clinician immediately Increase usual reliever (low-dose ICS-formoterol; increase frequency to max of 72 mcg formoterol/day; SABA: 2–6 puffs by MDI or 1 nebulizer treatment) If incomplete or poor response, repeat SABA immediately; proceed to the ED or call 911 if distress is severe and unresponsive to treatment Call 911 or go to the ED immediately if lips or fingernails are blue or gray or if there is trouble walking or talking because of shortness of breath Continue using SABA every 3–4 hr regularly for 24–48 hr

[a]OCS burst: prednisone (or equivalent) 40–60 mg/day for 5–7 days (adults) or 1–2 mg/kg/day (maximum 40 mg/day) for 3–5 days (children).

ED = emergency department; ICS = inhaled corticosteroid; MDI = metered dose inhaler; OCS = oral corticosteroid; PEFR = peak expiratory flow rate; SABA = short-acting β_2-agonist.

Q. Managing Exacerbations: Initial—Emergency Department (ED) or Hospital (Table 10)

Table 10. Classifying Severity of Asthma Exacerbations in the Urgent or Emergency Care Setting[a]

Severity	Symptoms and Signs	Initial PEF or FEV_1[b]	Clinical Course
Mild or moderate	Talks in phrases, prefers sitting to lying, respiratory rate increased, heart rate 100–120 beats/min, Sa_{O_2} (room air) 90%–95%	> 50% predicted or personal best	Usually cared for at home or office visit; relief from frequently inhaled SABA; likely short course of OCS; some symptoms last 1–2 days after treatment begins
Severe	Dyspnea at rest; interferes with conversation; sits hunched forward; agitated; heart rate > 120 beats/min; respiratory rate > 30 breaths/min; use of accessory muscles; Sa_{O_2} (room air) < 90%	≤ 50% of predicted or personal best	Usually requires ED visit and likely hospitalization Partial relief from frequent inhaled SABA Oral systemic corticosteroids; some symptoms last > 3 days after treatment is begun Adjunctive therapies are helpful
Life-threatening	Too dyspneic to speak, perspiring; drowsy; confused	< 25% of predicted or personal best	Requires ED or hospitalization, possible ICU Little or no relief from frequent inhaled SABAs IV corticosteroids Adjunctive therapies are helpful

[a]For all ages.

[b]Lung function measures (PEF or FEV_1) may be useful for children ≥ 5 yr but may not be attainable in children during an exacerbation.

ED = emergency department; ICU = intensive care unit; OCS = oral corticosteroid; PEF = peak expiratory flow; SABA = short-acting β_2-agonist..

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2022. Available at www.ginasthma.org/.

1. Mild to moderate exacerbation (FEV_1 of 50% or more)
   a. Oxygen to achieve oxygen saturation (Sa_{O_2}) of 93%–98% (greater than 95% in pregnant women and those with concomitant heart disease)
   b. Inhaled SABA (MDI with valved holding chamber or nebulizer) up to three doses in the first hour
      i. Adult dose: albuterol MDI 4–10 puffs every 20 minutes for up to 4 hours, then every 1–4 hours as needed or by nebulizer 2.5–5 mg every 20 minutes for three doses, then 2.5–10 mg every 1–4 hours as needed
      ii. Pediatric dose (12 years or younger): albuterol MDI 4–8 puffs every 20 minutes for three doses, then every 1–4 hours as needed; use holding chamber (add mask if younger than 4 years) or by nebulizer 0.15 mg/kg (minimal dose 2.5 mg) every 20 minutes for three doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed
   c. OCS if no response immediately or if patient recently took an OCS
2. Severe exacerbation (FEV_1 of 50% or less)
   a. Oxygen to achieve Sa_{O_2} of 93%–98% (more than 95% in pregnant women and those with concomitant heart disease)
   b. High-dose inhaled SABA plus ipratropium by MDI plus valved holding chamber or nebulizer every 20 minutes or continuously for 1 hour

c. Oral corticosteroids
   i. Adult dose: prednisone 40–50 mg/day in one or two divided doses until peak expiratory flow reaches 70% of predicted
   ii. Pediatric dose (12 years or younger): prednisone 1–2 mg/kg in two divided doses (maximum 40 mg/day) until peak expiratory flow reaches 70% of predicted
d. Consider adjunctive therapies (intravenous magnesium, intravenous ketamine, or heliox) if the patient is still unresponsive.

3. Impending or actual respiratory arrest
   a. Intubation and mechanical ventilation with oxygen 100%
   b. Nebulized SABA plus ipratropium
   c. Intravenous corticosteroids
   d. Consider adjunctive therapies (intravenous magnesium or heliox) if the patient is still unresponsive to therapy.
   e. Admission to intensive care

R. Managing Exacerbations: ED or Hospital After Repeat Assessment
1. Moderate exacerbation (FEV_1 greater than 50%)
   a. Inhaled SABA every 60 minutes
   b. Oral corticosteroid
   c. Continue treatment for 1–3 hours if improvement
2. Severe exacerbation (FEV_1 of 50% or less); no improvement after initial treatment
   a. Oxygen
   b. Nebulized SABA plus ipratropium; hourly or continuous
   c. Consideration of adjunctive therapies
3. If good response to above treatment and maintained for at least 60 minutes
   a. Continue inhaled SABA.
   b. Continue OCS course.
   c. Consider initiating an ICS (if patient is not already taking one).
   d. Discharge home.
4. If incomplete response, admit to hospital ward
   a. Continuation of inhaled SABA
   b. Systemic corticosteroids (oral or intravenous)
   c. Consideration of adjunctive therapies
5. If poor response, admit to intensive care
   a. Continuation of inhaled SABA, hourly or continuously
   b. Intravenous corticosteroid
   c. Consideration of adjunctive therapies
   d. Possible intubation and mechanical ventilation

Patient Case

4. A 25-year-old man presents to the ED with shortness of breath at rest. He is having trouble with conversation. He used 4 puffs of albuterol MDI at home, with no resolution of symptoms. His FEV_1 is 38% of predicted. Which therapy, in addition to oxygen, is best for him initially in the ED?

   A. Oxygen alone is sufficient.

   B. Give albuterol MDI 8 puffs every 20 minutes for 1 hour.

   C. Give albuterol plus ipratropium by nebulizer every 20 minutes for 1 hour, plus oral corticosteroids.

   D. Give albuterol plus ipratropium by nebulizer every 20 minutes for 1 hour, plus intravenous corticosteroids.

S. Additional Vaccines: Adults with asthma (19–64 years) should receive:
   1. One dose of 20-valent pneumococcal conjugate vaccine (PCV20) alone or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by one dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 1 year later.
   2. Influenza vaccine every fall or winter. Asthma in patients 5 years of age and older is considered a precaution for administration of the live, attenuated influenza vaccine (LAIV).

T. Asthma in Pregnancy
   1. Asthma may worsen, improve, or stay the same during pregnancy.
   2. Asthma may increase the risk of perinatal mortality, hyperemesis, vaginal hemorrhage, preeclampsia, complicated labor, neonatal mortality, prematurity, and low-birth-weight infants, especially if it is uncontrolled. Risks are small and are not shown in all studies.
   3. Medications
      a. The preferred controller is budesonide ICS; however, if asthma is well controlled on another ICS before pregnancy, it may be continued.
      b. The preferred rescue inhaler is albuterol.
      c. LABAs have less clinical experience. Use during pregnancy is reasonable if necessary for asthma control. Salmeterol is the preferred LABA.
      d. LTRAs have limited data; most data are with montelukast, and are reassuring. These are considered an alternative therapy.
      e. Prednisone: potential adverse effects in pregnancy are cleft palate, preeclampsia, gestational diabetes, low birth weight, and prematurity. However, few studies involved patients with asthma, and women might have been exposed to longer-term prednisone use. Prednisone should be used, if necessary, for acute exacerbations in pregnancy.

II. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Guidelines:

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2023. Available at www.goldcopd.org/.

A. Definition: COPD is a common, preventable, and treatable syndrome of persistent limitation in expiratory airflow encompassing both small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Airflow obstruction may be accompanied by airway hyperresponsiveness and may not be fully reversible. Airway and alveolar abnormalities are usually caused by significant exposure to noxious particles.
   1. Chronic bronchitis consists of persistent cough plus sputum production for most days of 3 months in at least 2 consecutive years and is an independent disease entity that may occur before or after the development of airflow limitation.
   2. Emphysema is abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. Emphysema is only one of several structural abnormalities in patients with COPD.

B. Diagnosis and Assessment
   1. The clinical diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with the presence of symptoms.
      a. Symptoms: Dyspnea (described by patients as "increased effort to breathe," "heaviness," "air hunger," or "gasping"), poor exercise tolerance, chronic cough, sputum production, wheezing

b. GOLD guidelines: Perform spirometry and consider COPD if a patient is older than 40 and has any of the following:
    i. Dyspnea that is progressive (worsens over time), persistent (present every day), and worse with exercise or on exertion
    ii. Chronic cough that is present intermittently or every day; often present throughout the day; seldom only nocturnal; may be nonproductive
    iii. Recurrent wheeze
    iv. Recurrent respiratory tract infections
    v. History of exposure to risk factors, especially tobacco smoke (most common risk factor), occupational dusts and chemicals, and smoke from home cooking and heating fuels
c. American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines: The single best predictor of airflow obstruction is the presence of all three of the following:
    i. Smoking history of more than 55 pack-years
    ii. Wheezing on auscultation
    iii. Patient's self-report of wheezing

2. For the diagnosis and assessment of COPD, spirometry is the gold standard.
    a. Spirometry revealing an FEV_1/FVC less than 70% of predicted is the hallmark of COPD. Bronchodilator reversibility testing is no longer recommended.
    b. Measurement of arterial blood gas tension should be considered for all patients with FEV_1 less than 50% of predicted or clinical signs suggestive of respiratory failure or right heart failure.
    c. On the basis of the spirometry result, a GOLD grade is assigned. The GOLD grade is primarily used to direct nonpharmacologic interventions (e.g., pulmonary rehabilitation, lung reduction surgery).
        i. GOLD 1: Mild FEV 80% or greater of predicted
        ii. GOLD 2: Moderate FEV 50%–79% of predicted
        iii. GOLD 3: Severe FEV 30%–49% of predicted
        iv. GOLD 4: Very severe FEV less than 30% of predicted
3. Assess the frequency of exacerbations in the past 12 months:
    a. Less severe: 0 or 1 exacerbation (not leading to hospital admission)
    b. More severe: 2 or more exacerbations, or 1 or more exacerbation leading to hospital admission
4. Use validated symptom scales or questionnaires:
    a. The COPD Assessment Test (CAT) measures health status impairment in COPD (www.catestonline.org).
        i. Measures symptoms beyond breathlessness, such as cough, sputum production, chest tightness, limitation of activities, sleep, energy level, and confidence to leave house
        ii. Scale of 5 to more than 30
            (a) 5 is upper limit of normal.
            (b) Less than 10 is low impact on life.
            (c) More than 30 is high impact on life; can barely leave the house
    b. mMRC breathlessness scale for assessing severity of breathlessness (Thorax 1999;54:581-6)
        i. Measures severity of shortness of breath or breathlessness
        ii. Scale of 0–4
            (a) 0 = least symptoms; breathless only with strenuous exercise
            (b) 4 = too breathless to leave house; breathless even when dressing

C. Factors Determining Severity of COPD
   1. Severity of airflow limitation (FEV_1)
   2. Frequency and severity of exacerbations
   3. Severity of symptoms (mMRC, CAT)
   4. Presence of comorbidities that may restrict activity (e.g., heart failure, heart disease, musculoskeletal disorders, depression)

D. Therapy Goals
   1. Relieve symptoms.
   2. Reduce the frequency and severity of exacerbations.
   3. Improve exercise tolerance.
   4. Improve health status.
   5. Minimize adverse effects from treatment.

E. Management of Stable COPD
   1. Description of levels of evidence or grades of recommendations (Table 11)

Table 11. Grades for Strength of Recommendations for COPD Guidelines

GOLD Guidelines	
A	Randomized clinical trials Rich body of data
B	Randomized clinical trials Limited body of data
C	Nonrandomized trials Observational studies
D	Panel judgment consensus

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

   2. Existing medications for COPD have not been shown to modify the long-term decline in lung function, the hallmark of this disease (level of evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms, complications, or both.
   3. Smoking cessation is a critical component of COPD management for patients who are actively using tobacco.
   4. Basic Principles of Pharmacotherapy
      a. Bronchodilator medications are central to the symptomatic management of COPD (level of evidence A).
      b. Primary mechanism of bronchodilators in COPD is through changes to smooth muscle tone that result in airway widening
      c. Bronchodilators can be given as needed or on a scheduled basis to prevent and reduce symptoms
      d. Principal bronchodilator treatments are: β_2-agonists, muscarinic antagonists, and a combination of these drugs
      e. Inhaled therapy is preferred to oral therapies because of less systemic exposure
      f. Combining agents from different classes may improve efficacy compared with increasing the dose of a single bronchodilator
      g. Short- or long-acting bronchodilator is recommended as initial treatment for all COPD groups (Table 12).

h. Treatment with a LAMA delays first exacerbation, reduces the overall number of COPD exacerbations and related hospitalizations, improves symptoms and health status (level of evidence A), and improves the effectiveness of pulmonary rehabilitation (level of evidence B).
   i. No effect on the rate of lung function decline (no consistent or significant FEV_1 improvement)
   ii. Initial tiotropium studies reported increased cardiovascular risk, but currently available studies do not reproduce the findings.

i. LABAs improve health status, quality of life, and FEV_1 and decrease COPD exacerbation rate (level of evidence A).
   i. No effect on mortality or rate of lung function decline
   ii. Do not have the same potential safety concerns as in asthma management
   iii. Salmeterol significantly reduces hospitalization rate and treatment of exacerbations (level of evidence B).
   iv. Indacaterol has significantly greater bronchodilator effect than salmeterol, similar to that of tiotropium (level of evidence A).

j. LAMAs versus LABAs
   i. POET-COPD trial: Tiotropium was more effective than salmeterol as initial bronchodilator therapy in moderate to very severe COPD regarding time to first exacerbation and annual number of exacerbations (N Engl J Med 2011;364:1093-103).
   ii. Cochrane review: Tiotropium is more effective than LABAs in preventing COPD exacerbations and COPD-related hospitalization, but not in overall hospitalizations or mortality. Symptom and lung function improvement were similar. However, studies are sparse. Fewer serious adverse events and withdrawals from studies occurred with tiotropium than with LABAs (Cochrane Database Syst Rev 2012;9:CD009157).
   iii. FLAME trial: LABA/LAMA (indacaterol/glycopyrrolate) had greater efficacy than LABA/ICS (salmeterol/fluticasone) in preventing COPD exacerbations in patients with a history of exacerbations in the previous year (N Engl J Med 2016;374:2222-34).

k. ICSs in Stable COPD
   i. Not recommended as monotherapy and may increase risk of mortality compared with use in combination treatment
   ii. Theoretically work as anti-inflammatory agents to decrease airway inflammation
   iii. Blood eosinophil counts may predict the magnitude of ICS effect in preventing future exacerbations
      (a) Some studies have found a greater risk of exacerbation after withdrawal of ICS when eosinophil count was greater than 300 cells/mcL (N Engl J Med 2014;371:1285-94; Am J Respir Crit Care Med 2018;198:329-39), whereas other studies have found no link between ICS withdrawal and increased exacerbation risk (Thorax 2005;60:480-7; Respir Res 2014;15:77).
      (b) Effect of an ICS on lung function, health status, and exacerbations is decreased when eosinophils are < 100 cells/mcL. Evidence is less clear regarding the efficacy of ICS with continued tobacco use.
   iv. Use is associated with an increased risk of pneumonia, oral candidiasis, and hoarse voice.
   v. Use of LABA/ICS in COPD is not encouraged. Triple therapy (LABA + LAMA + ICS) is preferred when ICS is indicated based on improved outcomes compared with LABA/ICS.
   vi. Group E: Consider LABA + LAMA + ICS if blood eosinophil count is ≥ 300 cells/mcL

l. Triple therapy:
   i. Shown to improve lung function and health-related quality of life while reducing the number of exacerbations
   ii. Two fixed-dose combination inhalers available (Table 6)

iii. The FULFIL trial showed improvements in FEV_1 and moderate to severe exacerbations with triple therapy compared to ICS/LABA Am J Respir Crit Care Med 2017;196:438-46).
iv. IMPACT further demonstrated benefits of triple therapy compared to ICS/LABA and LAMA/LABA through lower rate of moderate to severe COPD exacerbations compared to both dual treatments and lower rate of COPD hospitalizations than LAMA/LABA. N Engl J Med 2018;378:1671-80).
v. In certain patients, adding tiotropium to a LABA/ICS combination (triple therapy) improves lung function and health-related quality of life and reduces the number of exacerbations (level of evidence B).
vi. The ETHOS trial and a secondary analysis of IMPACT evaluated mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations as a prespecified outcome, although not the primary endpoint. All-cause mortality in the fixed-dose triple therapy arm was significantly lower compared to LABA/LAMA (only with higher dose ICS in ETHOS trial) and no differences were found in all-cause mortality when compared with LABA/ICS in both studies.

5. Patient assessment and selection of therapy
   a. GOLD guidelines combine symptoms (based on symptom scores) and frequency of exacerbations in the previous 12 months to determine patient risk group and recommend initial treatment (Figure 1 and Table 12).
   b. Maintenance therapy adjustments are recommended according to the predominant treatable trait of dyspnea (Table 13) or exacerbations (Table 14). These recommendations do not depend on the ABE assessment at diagnosis and focus on current treatment. If both exacerbations and dyspnea need to be targeted, the exacerbation pathway should be followed.
   c. De-escalation strategies are suggested for patients who experience adverse effects or lack of clinical efficacy with ICS or generally have symptom improvement that may require less therapy.
   d. Peak inspiratory flow rate (PIFR) measured against the simulated resistance of a dry powder inhaler (DPI) is emerging as a way to further guide therapy and provide a patient-centered product recommendation. PIFR less than 60 mL/minute is considered suboptimal and may identify those with a suboptimal response to a DPI.

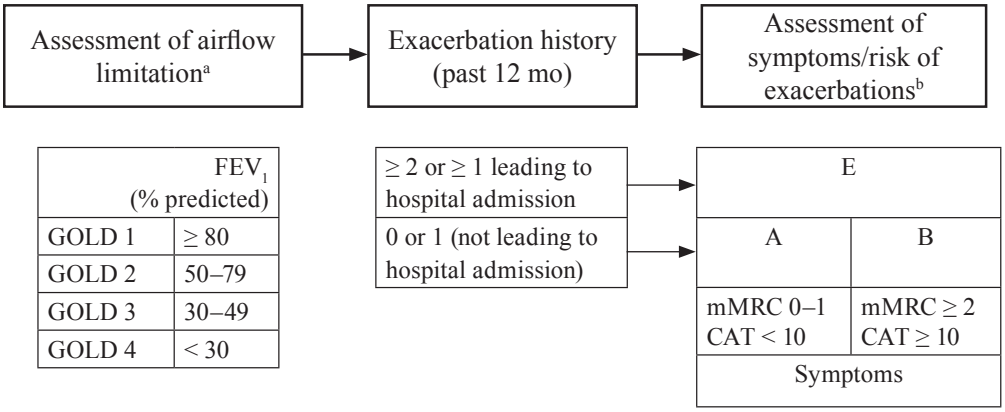


Figure 1. GOLD guidelines: refined assessment of COPD severity and risk.

[a]Post-bronchodilator FEV_1 should be used.

[b]CAT score is preferred, but any can be used.

CAT = COPD Assessment Test (validated questionnaire); GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council breathlessness scale (validated questionnaire).

Adapted from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2023 Update. Available at www.goldcopd.org/.

Table 12. GOLD Guidelines: Initial Pharmacologic Treatment

Patient Group	Symptoms and Exacerbations	Recommended Initial Treatment
A	Few symptoms (CAT score < 10) No hospitalizations ≤ 1 exacerbation in the past year	Bronchodilator (short- or long-acting)
B	Many symptoms (CAT score ≥ 10) No hospitalizations ≤ 1 exacerbations in the past year	LABA + LAMA[a]
E	Few or many symptoms ≥ 1 COPD-related hospitalization or ≥ 2 exacerbations in the past year	LABA + LAMA[a] LABA + LAMA +ICS[a,b]

[a]Single inhaler may be more convenient and effective than multiple inhalers.

[b]Consider if eosinophils ≥ 300 cells/mcL.

CAT = COPD Assessment Test (validated questionnaire); COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2023.

Table 13. Maintenance Therapy Modifications for the Predominant Treatable Trait of Dyspnea

Current Treatment	Recommended Treatment Change(s)
LABA or LAMA	LABA + LAMA[a] If ineffective: consider changing inhaler devices or molecules, and investigate other causes of dyspnea
LABA + LAMA[a]	Consider changing inhaler devices or molecules, implement or escalate nonpharmacologic treatments or investigate and treat other causes of dyspnea

[a]Single inhaler may be more convenient and effective than multiple inhalers.

LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2023.

Table 14. Maintenance Therapy Modifications for the Predominant Treatable Trait of Exacerbations

Current Treatment	Recommended Treatment Change(s)
LABA or LAMA	LABA + LAMA[a] (if blood eosinophils < 300 cells/mcL OR LABA + LAMA + ICS[a] (if blood eosinophils ≥ 300 cells/mcL)
LABA + LAMA	LABA + LAMA + ICS[a] (if blood eosinophils ≥ 100 cells/mcL) OR If blood eosinophils < 100 cells/mcL, consider adding roflumilast if FEV_1 < 50% and chronic bronchitis AND/OR azithromycin daily if former smoker
LABA + LAMA + ICS	Consider de-escalation of ICS and change to LABA + LAMA[b] OR Consider adding roflumilast if FEV_1 < 50% and chronic bronchitis AND/OR azithromycin daily if former smoker

[a]Single inhaler may be more convenient and effective than multiple inhalers.

[b]Consider if pneumonia, or other considerable adverse effects. De-escalation is more likely to be associated with future exacerbations if blood eosinophil count is ≥ 300 cells/mcL.

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2023.

6. Other pharmacologic treatments
    a. Phosphodiesterase type 4 (PDE-4) inhibitor: roflumilast (Daliresp)
        i. Indication: PDE-4 inhibitors may be used as a daily treatment to reduce the risk of COPD exacerbations in patients with severe COPD (FEV_1 less than 50% of predicted) associated with chronic bronchitis and a history of frequent exacerbations despite treatment with LABA + LAMA + ICS, particularly if eosinophils are less than 100 cells/mcL. Studies show a reduction in exacerbations and a reduction in the composite end point of moderate exacerbations treated with oral or systemic corticosteroids or severe exacerbations necessitating hospitalization or causing death (level of evidence B). These effects also occur when roflumilast is added to LA bronchodilators (level of evidence B). No trials have assessed the effects of roflumilast on COPD exacerbations when added to an ICS/LA bronchodilator combination. No comparison of adding roflumilast versus ICS to LA bronchodilators is available (now being studied).
        ii. Reduces inflammation through inhibition of the breakdown of intracellular cyclic adenosine monophosphate; has no direct bronchodilator activity
        iii. Starting dose: 250 mcg orally once daily for four weeks and then increased to the maintenance dose of 500 mcg orally once daily, which may allow for better GI tolerance
        iv. Contraindicated in cases of moderate to severe liver impairment and in nursing mothers
        v. Can cause weight loss (monitor) and psychiatric events, including suicidality (monitor; weigh risk-benefit ratio in patients with preexisting psychiatric illness). Twenty percent of patients studied had weight loss of 5%–10% of body weight, compared with 7% with placebo; average weight loss was 2 kg.
        vi. Adverse reactions include diarrhea, weight loss or decreased appetite, nausea, headache, back pain, influenza, insomnia, and dizziness.

vii. Use with strong cytochrome P450 (CYP) enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended; use with CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine) increases roflumilast exposure and adverse effects (weigh risk-benefit ratio).
viii. According to the ACCP/CTS guidelines to prevent exacerbations, roflumilast is suggested for patients with moderate-severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the past year.

b. Antibiotics – azithromycin
   i. Actions are anti-inflammatory and antibacterial
   ii. Daily azithromycin at 250 mg orally daily for 1 year found to lengthen time to first exacerbation, decrease overall exacerbation rate, and improve quality of life (N Engl J Med 2011;365:689-98)
   iii. Azithromycin 500 mg orally 3 times per week and erythromycin 500 mg orally twice daily have reduced exacerbations (Lancet Respir Med 2014;2:361-8; N Engl J Med 2011;365:689-98)
   iv. Potential adverse effects include hearing loss (contradictory evidence), pneumonia, GI disturbances, and QTc prolongation
   v. Recommended as add-on to treatment intensification with LABA + LAMA +/- ICS if eosinophils < 100 cells/mcL and former smoker
c. Smoking cessation therapy (essential for all patients)
d. Vaccinations
   i. Influenza vaccine annually (essential for all patients)
   ii. Adults aged 19-64 years with COPD should receive one dose of PCV20 alone or one dose of PCV15 followed by one dose of PPSV23 at least 1 year later.
   iii. Tdap vaccination should be provided to patients with COPD to protect against tetanus, diphtheria, and pertussis if not vaccinated during adolescence.
   iv. COVID-19 vaccination according to CDC guidelines
   v. Shingles vaccination according to CDC guidelines
e. α_1-Antitrypsin augmentation therapy (level of evidence B)
   i. Once weekly intravenous therapy of an α_1-proteinase inhibitor (Aralast NP, Glassia, Prolastin-C, Zemaira)
   ii. For young patients with a severe hereditary α_1-antitrypsin deficiency and established emphysema.
   iii. Patients with an α_1-antitrypsin deficiency are usually white, have COPD at a young age (younger than 45), and have a strong family history. It may be worthwhile to screen patients with these characteristics for α_1-antitrypsin deficiency.
   iv. α_1-Antitrypsin deficiency should be considered in patients with frequent COPD exacerbations (Cleve Clin J Med 2016;83:507-14).

Patient Cases

5. A 62-year-old man was recently given a diagnosis of COPD. Spirometry reveals an FEV_1/FVC 60% of predicted, pre-bronchodilator FEV_1 70% of predicted, and post-bronchodilator FEV_1 72% of predicted. His symptoms are quite bothersome. He has an mMRC score of 2. He had 1 exacerbation in the past year that did not require hospitalization. In addition to albuterol 2 puffs every 4–6 hours as needed, which pharmacotherapy option is most appropriate to initiate?
   A. Tiotropium 2.5 mg 2 puffs once daily.
   B. Salmeterol 50 mcg 1 puff twice daily.
   C. Tiotropium/olodaterol 2.5/2.5 2 puffs once daily.
   D. Fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/25 mcg 1 inhalation once daily.

6. A 52-year-old woman with COPD reports a gradual worsening of shortness of breath during the past few years. Spirometry reveals FEV_1/FVC 55% and FEV_1 63% of predicted. Her CAT score is 10 and eosinophil count is 68 cells/mcL. She has not had a COPD exacerbation or received systemic corticosteroids in the past 2 years. Her current COPD medications are tiotropium inhaler once daily and albuterol HFA as needed. According to the GOLD guidelines, which is the most appropriate course of action?
   A. Adding salmeterol 50 mcg 1 puff twice daily.
   B. Adding long-term azithromycin 250 mg once daily.
   C. Adding fluticasone 110 mcg 2 puffs twice daily.
   D. Discontinuing tiotropium and initiating salmeterol/fluticasone 50 mcg/250 mcg 1 puff twice daily.

7. Nonpharmacologic therapy
   a. Home oxygen therapy
      i. Recommended in patients who have a Pa_{O_2} of 55 mm Hg or less (or 55–60 mm Hg if pulmonary hypertension, peripheral edema, or polycythemia [level of evidence D]) or Sa_{O_2} of 88% or less, with or without hypercapnia, confirmed twice during a 3-week period (level of evidence B)
      ii. Improved survival with long-term (more than 15 hours/day) use in patients with chronic respiratory failure
   b. Pulmonary rehabilitation (essential for patient groups B–D; level of evidence A)
      i. Includes exercise training, nutrition counseling, and education
      ii. Recommended when patients have moderate COPD instead of waiting until it is more severe
      iii. Improves many outcomes in COPD, including quality of life and survival
   c. Lung cancer screening
      i. USPSTF recommends annual lung cancer screening for aged 55-80 years old who have a 30 pack-year smoking history and currently smoke or quit < 15 years ago.
      ii. Concern related to appropriateness of recommendations as lung cancer is leading cause of death in patients with COPD
      iii. It has been suggested to change to a > 1 pack-year threshold for patients with COPD to lead to a higher life expectancy than currently seen (Cancer 2015;121:1556-62).
8. Other medications
   a. β-Blockers
      i. Observational data suggest that long-term treatment with β-blockers reduces risk of exacerbations and improves survival, even in patients without overt cardiovascular disease (Arch Intern Med 2010;170:880-7).
         (a) More than half of the patients studied had cardiovascular risk factors or coronary artery disease.
         (b) Mostly cardioselective β-blockers were used.

ii. β-Blockers should not currently be recommended for the treatment of COPD, but β-blockers should not be withheld in patients with COPD who also have heart disease, chronic heart failure, or other cardiovascular conditions in which β-blockers are beneficial (Cochrane Database Syst Rev 2005;4:CD003566).
iii. The mechanism of benefit in COPD is unknown, but β-blockers can upregulate β_2-receptors in the lungs, which may improve the effectiveness of inhaled β-agonists.

b. Statins
i. Several retrospective studies have found benefits for statin use in COPD for reducing exacerbations and COPD-related mortality (Thorax 2015;70:33-40; Am J Respir Crit Care Med 2013;187:A6017; Am J Med 2013;126:598-606).
ii. The STATCOPE trial found no significant effect of simvastatin on the number of severe COPD exacerbations per person-year compared with placebo (Chest 2015;147:894-942).
iii. The Rotterdam trial found a 78% lower risk of mortality in patients with COPD and high-sensitivity C-reactive protein concentrations greater than 3 mg/dL, indicating a higher level of systemic inflammation (Pulm Pharmacol Ther 2013;26:212-7).
iv. Authors of a meta-analysis involving 53 studies concluded that statins significantly reduced the risk of all-cause mortality by 28%, risk of COPD-associated mortality by 28%, and risk of acute COPD exacerbations by 16%. Authors hypothesized that statins decrease many inflammatory markers thought to play a role in COPD (CRP, IL-6, IL-8 and TNFα) (Respir Res 2019;20:Article 17).
v. No strong prospective evidence exists to suggest statins provide a clinical benefit in patients with COPD without other cardiovascular disease risk factors.

F. Management of Acute Exacerbations of Chronic COPD
1. A COPD exacerbation is an acute worsening of a patient's baseline respiratory symptoms (e.g., dyspnea, cough, and/or an increase in quantity or purulence of sputum) that is worse than normal day-to-day variation and results in a change in medication. Diagnosis is based purely on clinical presentation.
2. Classification:
a. Mild: SA bronchodilators only
b. Moderate: SA bronchodilators plus antibiotics and/or oral corticosteroids
c. Severe: hospitalization or ED visits
i. No respiratory failure: respiratory rate of 20 to 30 breaths/minute; no accessory muscles; no mental status changes; hypoxemia improved with supplemental oxygen; no increase in $PaCO_2$
ii. Acute respiratory failure, non–life-threatening: more than 30 breaths/minute; accessory respiratory muscles in use; no change in mental status; hypoxemia improved with supplemental oxygen; $PaCO_2$ increased compared to baseline
iii. Acute respiratory failure, life-threatening: more than 30 breaths/minute; accessory respiratory muscles in use; acute changes in mental status; hypoxemia not improved with supplemental oxygen; $PaCO_2$ increased compared to baseline or pH of 7.25 or greater
3. Common precipitating factors include infection of the tracheobronchial tree and viral upper respiratory tract infections (most common) and air pollution. However, the cause of one-third of exacerbations cannot be determined.
4. Spirometry is inaccurate during an exacerbation and is not recommended.
5. Pulse oximetry can be used to determine the need for supplemental oxygen, which should be given in severe exacerbations. In exacerbations necessitating hospitalization, arterial blood gas measurement should be performed. Supplemental oxygen should be titrated to a target saturation of 88%–92% (BMJ 2010;341:c5462).

6. Inhaled bronchodilators (inhaled SABAs with or without SA anticholinergics) are the preferred treatment of COPD exacerbations (level of evidence C).
    a. The usual dose of albuterol is 2.5 mg by nebulizer every 1 to 4 hours as needed or 4 to 8 puffs by MDI with holding chamber every 1 to 4 hours as needed.
    b. SA anticholinergics (ipratropium) are generally added for acute exacerbations.
7. Systemic corticosteroids are effective, and they shorten recovery time, improve FEV_1, and improve hypoxemia (level of evidence A). They also lower the risk of treatment failure and early relapse rate and shorten hospital stays. Systemic corticosteroids should be used in most exacerbations. OCS dose for outpatient treatment: 40 mg of oral prednisone once daily for 5 days is recommended in the GOLD guidelines (level of evidence B), but insufficient data are available to provide strong conclusions about the optimal duration.
    a. Higher daily doses or oral prednisone/prednisolone may be used (e.g., 50–60 mg daily).
    b. Studies have demonstrated that in patients with a COPD exacerbation, a shorter course of systemic corticosteroids (5 days) was non-inferior to a longer (14 days) course with respect to re-exacerbation (JAMA 2013;309:2223-31; Cochrane Database Syst Rev 2018;3:1-65.).
8. Antibiotic treatment should be initiated for exacerbations if the criteria below are met. The most common pathogens in COPD exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In patients with GOLD 3 and 4 severity, *Pseudomonas aeruginosa* should be considered a potential pathogen.
    a. The three cardinal symptoms in COPD exacerbations are: increased dyspnea, increased sputum volume, and increased sputum purulence.
        i. Antibiotics should be given if all three cardinal symptoms are present (level of evidence B).
        ii. Antibiotics should be given if two of the three cardinal symptoms are present and if increased sputum purulence is one of the symptoms (level of evidence C).
        iii. Antibiotics should be given to patients with severe exacerbations requiring mechanical ventilation (level of evidence B).
    b. The recommended duration of antibiotic treatment is usually 5 to 7 days (level of evidence B).
    c. Recommended antibiotics
        i. Empiric treatment consists of amoxicillin with clavulanic acid, a macrolide (e.g., azithromycin), or a tetracycline (e.g., doxycycline). Antibiotic selection should be decided on using local susceptibility data and trends.
        ii. If antibiotics have been used recently (in the last 3 months), use an alternative class.
        iii. In complicated COPD with risk factors, amoxicillin/clavulanate, levofloxacin, and moxifloxacin are antibiotics of choice. Risk factors include comorbid diseases, severe COPD (FEV_1 less than 50% of predicted), more than three exacerbations/year, antibiotic use in past 3 months
        iv. If the patient is at risk of *Pseudomonas* infection: Obtain sputum culture(s) and administer high-dose levofloxacin (750 mg) or ciprofloxacin. Risk factors include: Four or more antibiotic courses within the past year, recent hospitalization (in the past 90 days), isolation of *Pseudomonas* during past hospitalization(s), severe COPD (FEV_1 less than 50% of predicted)
        v. If exacerbation does not respond to the initial antibiotic, sputum culture and sensitivity should be performed.

Patient Case

7. A 64-year-old woman with COPD in GOLD patient group A presents for a clinic visit. In the past few days, she has had a worsening of shortness of breath and a productive cough with more "cloudy" and more copious sputum than usual. Pulse oximetry is 95% on room air. She has a nebulizer at home. In addition to regular use of albuterol plus ipratropium by nebulizer every 1 to 4 hours, which is the best course of action?

   A. No additional therapy is necessary.

   B. Add oral prednisone 40 mg once daily for 5 days.

   C. Add azithromycin 500 mg daily for 3 days.

   D. Add oral prednisone 40 mg once daily for 5 days and azithromycin 500 mg daily for 3 days.

Note: The following figures were developed by the CDC. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. These charts are available on the agency website for no charge.

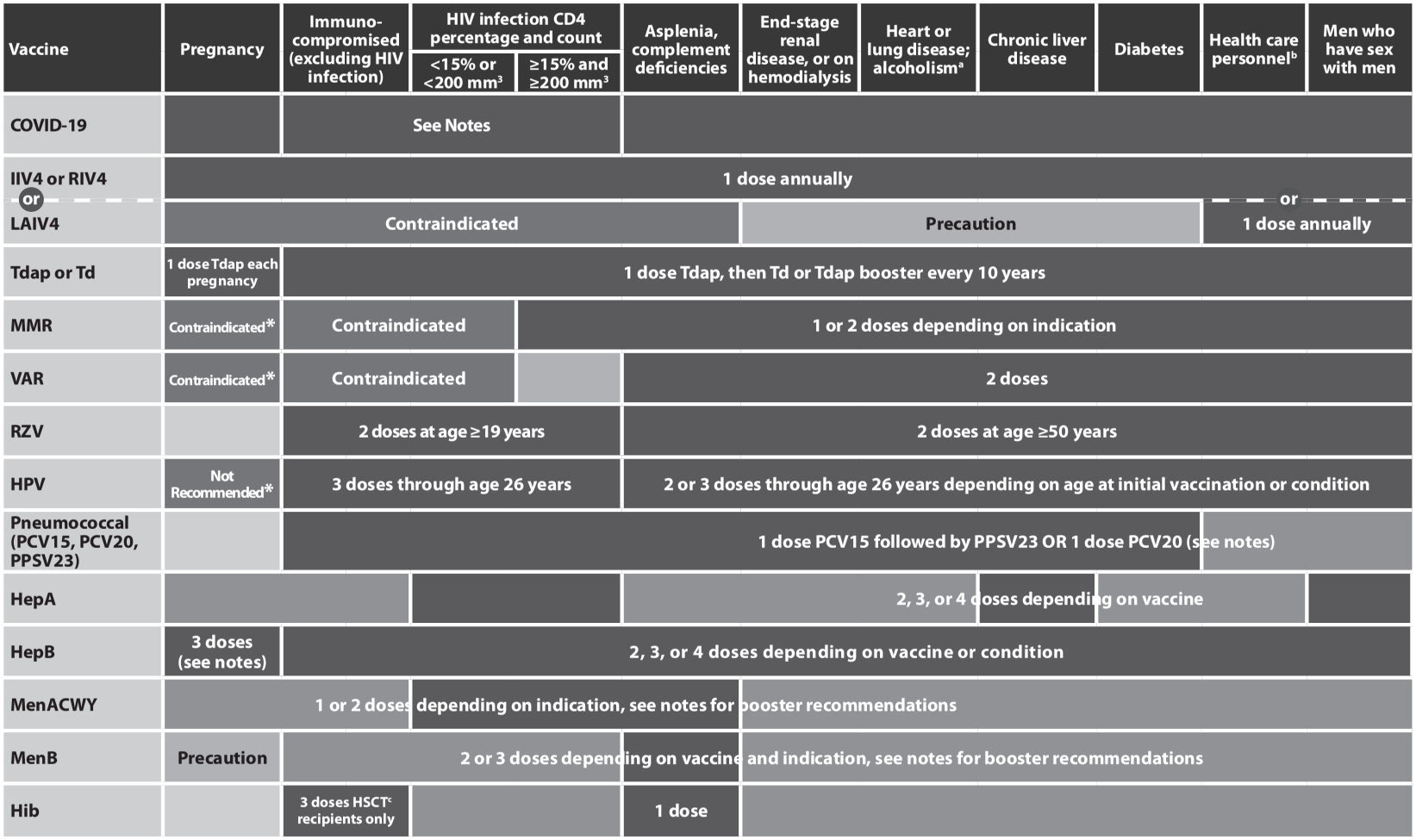
III. ADULT IMMUNIZATIONS

Vaccine
19–26 years
27–49 years
50–64 years
≥65 years
COVID-19
2- or 3- dose primary series and booster (See Notes)
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)
or
Influenza live, attenuated (LAIV4)
1 dose annually
or
1 dose annually
Tetanus, diphtheria, pertussis (Tdap or Td)
1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)
1 dose Tdap, then Td or Tdap booster every 10 years
Measles, mumps, rubella (MMR)
1 or 2 doses depending on indication (if born in 1957 or later)
For healthcare personnel, see notes
Varicella (VAR)
2 doses (if born in 1980 or later)
2 doses
Zoster recombinant (RZV)
2 doses for immunocompromising conditions (see notes)
2 doses
Human papillomavirus (HPV)
2 or 3 doses depending on age at initial vaccination or condition
27 through 45 years
Pneumococcal (PCV15, PCV20, PPSV23)
1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)
See Notes
See Notes
Hepatitis A (HepA)
2, 3, or 4 doses depending on vaccine
Hepatitis B (HepB)
2, 3, or 4 doses depending on vaccine or condition
Meningococcal A, C, W, Y (MenACWY)
1 or 2 doses depending on indication, see notes for booster recommendations
Meningococcal B (MenB)
2 or 3 doses depending on vaccine and indication, see notes for booster recommendations
19 through 23 years
Haemophilus influenzae type b (Hib)
1 or 3 doses depending on indication
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Recommended vaccination based on shared clinical decision-making
No recommendation/ Not applicable

Figure 2. Recommended adult immunization scheduleby age group,[a] United States, 2023.

[a]The above recommendations must be read together with the footnotes on the following pages of this schedule.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule by Age Group, United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult.


Vaccine
Pregnancy
Immuno-compromised (excluding HIV infection)
HIV infection CD4 percentage and count
<15% or <200 mm³
≥15% and ≥200 mm³
Asplenia, complement deficiencies
End-stage renal disease, or on hemodialysis
Heart or lung disease; alcoholism[a]
Chronic liver disease
Diabetes
Health care personnel[b]
Men who have sex with men
COVID-19
See Notes
IIV4 or RIV4
or
LAIV4
1 dose annually
or
Contraindicated
Precaution
1 dose annually
Tdap or Td
1 dose Tdap each pregnancy
1 dose Tdap, then Td or Tdap booster every 10 years
MMR
Contraindicated*
Contraindicated
1 or 2 doses depending on indication
VAR
Contraindicated*
Contraindicated
2 doses
RZV
2 doses at age ≥19 years
2 doses at age ≥50 years
HPV
Not Recommended*
3 doses through age 26 years
2 or 3 doses through age 26 years depending on age at initial vaccination or condition
Pneumococcal (PCV15, PCV20, PPSV23)
1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)
HepA
2, 3, or 4 doses depending on vaccine
HepB
3 doses (see notes)
2, 3, or 4 doses depending on vaccine or condition
MenACWY
1 or 2 doses depending on indication, see notes for booster recommendations
MenB
Precaution
2 or 3 doses depending on vaccine and indication, see notes for booster recommendations
Hib
3 doses HSCT[c] recipients only
1 dose
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Recommended vaccination based on shared clinical decision-making
Precaution–vaccination might be indicated if benefit of protection outweighs risk of adverse reaction
Contraindicated or not recommended–vaccine should not be administered.
*Vaccinate after pregnancy.
No recommendation/ Not applicable

a. Precaution for LAIV4 does not apply to alcoholism. **b.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **c.** Hematopoietic stem cell transplant.

Figure 3. Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2023.

[a]The above recommendations must be read together with the footnotes on the following pages of this schedule.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2023

For vaccine recommendations for persons 18 years of age or younger, see the Recommended Child and Adolescent Immunization Schedule.

COVID-19 vaccination

Routine vaccination

- **Primary series:** 2-dose series at 0, 4-8 weeks (Moderna) or 2-dose series at 0, 3-8 weeks (Novavax, Pfizer-BioNTech)
- **Booster dose:** see www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

Special situations

Persons who are moderately or severely immunocompromised

- **Primary series**
  - 3-dose series at 0, 4, 8 weeks (Moderna) or 3-dose series at 0, 3, 7 weeks (Pfizer-BioNTech)
  - 2-dose series at 0, 3 weeks (Novavax)
- **Booster dose:** see www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html
- **Pre-exposure prophylaxis (e.g., monoclonal antibodies)** may be considered to complement COVID-19 vaccination. See www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

For Janssen COVID-19 Vaccine recipients see COVID-19 schedule at www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html.

Note: Current COVID-19 schedule available at www.cdc.gov/vaccines/covid-19/downloads/COVID-19-immunization-schedule-ages-6months-older.pdf. For more information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, please visit www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

Haemophilus influenzae type b vaccination

Special situations

- **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose preferably at least 14 days before splenectomy
- **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])

Special situations

- **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
  - **Chronic liver disease** (e.g., persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - **HIV infection**
  - **Men who have sex with men**
  - **Injection or noninjection drug use**
  - **Persons experiencing homelessness**
  - **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatitis A virus infection
  - **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months)
  - **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy
  - **Settings for exposure,** including health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally disabled persons (individual risk factor screening not required)

Hepatitis B vaccination

Routine vaccination

- **Age 19 through 59 years: complete a 2- or 3- or 4-dose series**
  - 2-dose series only applies when 2 doses of Heplisav-B* are used at least 4 weeks apart
  - 3-dose series Engerix-B, PreHevbrio*, or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks])
  - 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months])
  - 4-dose series HepA-HepB (Twinrix) accelerated schedule of 3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months

***Note:** Heplisav-B and PreHevbrio are not recommended in pregnancy due to lack of safety data in pregnant persons.

Figure 4. Footnotes from adult immunization schedule, United States, 2023.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule for Ages 19 Years and Older: United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2023

- **Age 60 years or older with** known risk factors for hepatitis B virus infection **should** complete a HepB vaccine series.
- **Age 60 years or older without** known risk factors for hepatitis B virus infection **may** complete a HepB vaccine series.
  - **Risk factors for hepatitis B virus infection include:**
    - **Chronic liver disease** (e.g., persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
    - **HIV infection**
    - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
    - **Current or recent injection drug use**
    - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis; patients with diabetes)
    - **Incarceration**
    - **Travel in countries with high or intermediate endemic hepatitis B**

Special situations

- **Patients on dialysis:** complete a 3- or 4-dose series
  - 3-dose series Recombivax HB at 0, 1, 6 months (note: use Dialysis Formulation 1 mL = 40 mcg)
  - 4-dose series Engerix-B at 0, 1, 2, and 6 months (note: use 2 mL dose instead of the normal adult dose of 1 mL)

Human papillomavirus vaccination

Routine vaccination

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depending on age at initial vaccination or condition:
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
  - **Age 9–14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart:** 1 additional dose
  - **Age 9–14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV vaccination series complete, no additional dose needed
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted
- **No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.**

Shared clinical decision-making

- **Some adults age 27–45 years:** Based on shared clinical decision-making, 2- or 3-dose series as above

Special situations

- **Age ranges recommended above for routine and catch-up vaccination or shared clinical decision-making also apply in special situations**
  - **Immunocompromising conditions, including HIV infection**: 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
  - **Pregnancy**: Pregnancy testing is not needed before vaccination; HPV vaccination is not recommended until after pregnancy; no intervention needed if inadvertently vaccinated while pregnant

Influenza vaccination

Routine vaccination

- **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annually.
  - **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is available, then any other age-appropriate influenza vaccine should be used.
- For the 2022–2023 season, see www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm
- For the 2023–2024 season, see the 2023–2024 ACIP influenza vaccine recommendations.

Special situations

- **Egg allergy, hives only:** any influenza vaccine appropriate for age and health status annually
- **Egg allergy–any symptom other than hives** (e.g., angioedema, respiratory distress or required epinephrine or another emergency medical intervention): Any influenza vaccine appropriate for age and health status may be administered. If using egg-based IIV4 or LAIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions.
- **Close contacts (e.g., caregivers, healthcare workers) of severely immunosuppressed persons who require a protected environment:** these persons should not receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppressed persons for 7 days after vaccination.
- **Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine:** see Appendix listing contraindications and precautions

Figure 4. Footnotes from adult immunization schedule, United States, 2023. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule for Ages 19 Years and Older: United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2023

- **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** Generally, should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza

Measles, mumps, and rubella vaccination

Routine vaccination

- **No evidence of immunity to measles, mumps, or rubella:** 1 dose
  - **Evidence of immunity:** Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose
- **Nonpregnant persons of childbearing age with no evidence of immunity to rubella:** 1 dose
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 for at least 6 months and no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm^3
- **Severe immunocompromising conditions:** MMR contraindicated
- **Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR
- **In mumps outbreak settings,** for information about additional doses of MMR (including 3rd dose of MMR), see www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm
- **Health care personnel:**
  - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider 2-dose series at least 4 weeks apart for protection against measles or mumps or 1 dose for protection against rubella
  - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart for protection against measles or mumps or at least 1 dose for protection against rubella

Meningococcal vaccination

Special situations for MenACWY

- **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains
- **Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologists routinely exposed to *Neisseria meningitidis*:** 1 dose MenACWY (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains
- **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:** 1 dose MenACWY (Menactra, Menveo, or MenQuadfi)
- For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Shared clinical decision-making for MenB

- **Adolescents and young adults age 16–23 years (age 16–18 years preferred) not at increased risk for meningococcal disease:** Based on shared clinical decision-making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Trumenba) at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

Special situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidis*:** 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a fourth dose should be administered at least 4 months after dose 3); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks
- For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting (e.g., in community or organizational settings and among men who have sex with men) and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm

Note: MenB vaccines may be administered simultaneously with MenACWY vaccines if indicated, but at a different anatomic site, if feasible.

Figure 4. Footnotes from adult immunization schedule, United States, 2023. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule for Ages 19 Years and Older: United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2023

Pneumococcal vaccination

Routine vaccination

- **Age 65 years or older who have:**
  - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown:** 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition,* cochlear implant, or cerebrospinal fluid leak to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups.
  - **Previously received only PCV7:** follow the recommendation above.
  - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR complete the recommended PPSV23 series as described here www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
  - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPSV23 dose. If PCV15 is used, it need not be followed by another dose of PPSV23.
  - **Previously received both PCV13 and PPSV23 but NO PPSV23 was received at age 65 years or older:** 1 dose PCV20 at least 5 years after their last pneumococcal vaccine dose OR complete the recommended PPSV23 series as described here www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
  - **Previously received both PCV13 and PPSV23, AND PPSV23 was received at age 65 years or older:** Based on shared clinical decision-making, 1 dose of PCV20 at least 5 years after the last pneumococcal vaccine dose.
- For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

Special situations

- **Age 19–64 years with certain underlying medical conditions or other risk factors** who have**
  - **Not previously received a PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown:** 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition,* cochlear implant, or cerebrospinal fluid leak
  - **Previously received only PCV7:** follow the recommendation above.
  - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR complete the recommended PPSV23 series as described here www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
  - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPSV23 dose. If PCV15 is used, it need not be followed by another dose of PPSV23.
  - **Previously received both PCV13 and PPSV23 but have not completed the recommended series:** 1 dose PCV20 at least 5 years after their last pneumococcal vaccine dose OR complete the recommended PPSV23 series as described here www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
- For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

*__Note:__ Immunocompromising conditions include chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies.

**__Note:__ Underlying medical conditions or other risk factors include alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smoking, cochlear implant, congenital or acquired asplenia, CSF leak, diabetes mellitus, generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatrogenic immunosuppression, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, solid organ transplants, or sickle cell disease or other hemoglobinopathies.

Polio vaccination

Routine vaccination

Routine poliovirus vaccination of adults residing in the United States is not necessary.

Special situations

- **Adults at increased risk of exposure to poliovirus with:**
  - No evidence of a complete polio vaccination series (i.e., at least 3 doses): administer remaining doses (1, 2, or 3 doses) to complete a 3-dose series
  - Evidence of completed polio vaccination series (i.e., at least 3 doses): may administer one lifetime IPV booster

For detailed information, see: www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html

Figure 4. Footnotes from adult immunization schedule, United States, 2023. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule for Ages 19 Years and Older: United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2023

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

- **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10 years

Special situations

- **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks later, and a third dose of Td or Tdap 6–12 months later (Tdap can be substituted for any Td dose, but preferred as first dose), Td or Tdap every 10 years thereafter
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm

Varicella vaccination

Routine vaccination

- **No evidence of immunity to varicella:** 2-dose series 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose
  - **Evidence of immunity:** U.S.-born before 1980 (except for pregnant persons and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm³ with no evidence of immunity:** Vaccination may be considered (2 doses 3 months apart); VAR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm³
- **Severe immunocompromising conditions:** VAR contraindicated

Zoster vaccination

Routine vaccination

- **Age 50 years or older*:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination.

***Note:** Serologic evidence of prior varicella is not necessary for zoster vaccination. However, if serologic evidence of varicella susceptibility becomes available, providers should follow ACIP guidelines for varicella vaccination first. RZV is not indicated for the prevention of varicella, and there are limited data on the use of RZV in persons without a history of varicella or varicella vaccination.

Special situations

- **Pregnancy:** There is currently no ACIP recommendation for RZV use in pregnancy. Consider delaying RZV until after pregnancy.
- **Immunocompromising conditions (including persons with HIV regardless of CD4 count)**:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon). For detailed information, see www.cdc.gov/shingles/vaccination/immunocompromised-adults.html

****Note:** If there is no documented history of varicella, varicella vaccination, or herpes zoster, providers should refer to the clinical considerations for use of RZV in immunocompromised adults aged ≥19 years and the ACIP varicella vaccine recommendations for further guidance: www.cdc.gov/mmwr/volumes/71/wr/mm7103a2.htm

Figure 4. Footnotes from adult immunization schedule, United States, 2023. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Adult Immunization Schedule for Ages 19 Years and Older: United States, 2023. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

A. General Immunization Guidelines
   1. Basic recommendations for adult immunization are based on age and specific vaccines (see Figures 2 and 4).
   2. Certain medical conditions require special consideration when determining whether additional immunizations are recommended (see Figure 3 and footnotes).
   3. On the basis of patient-specific factors, specific vaccines or formulations should be avoided or used with caution.

B. Contraindications and Precautions
   1. Do not administer a vaccine when a contraindication is present due to an increased risk for a serious adverse reaction.
      a. Live vaccines should generally be avoided in patients who are severely immunocompromised.
      b. Pregnant women should not receive live, attenuated vaccines due to theoretical risk to the fetus.
   2. In general, vaccines should be deferred if a precaution is present based on the risk of experiencing a more severe reaction to the vaccine (this risk is less severe than with a contraindication).
      a. A vaccine can be administered when a precaution is present if the benefit outweighs the risks.
      b. All vaccines have a precaution for administration in a patient with a moderate or severe acute illness (with or without fever).
   3. Full lists of contraindications and precautions are available in package inserts or within the Advisory Committee on Immunization Practices (ACIP) Best Practice Guidelines for Immunizations (www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html).

C. Major Changes in the 2023 Adult Immunization Schedule
   1. COVID-19 vaccines were added to the schedule.
   2. New abbreviations added for COVID-19 vaccines: 1vCOV-mRNA, 2vCOV-mRNA, and 1vCOV-aPS
      a. Valency: 1v and 2v = monovalent and bivalent, respectively
      b. Platform: mRNA or acellular protein subunit "aPS"
   3. Updated shared clinical decision-making option for pneumococcal vaccines

D. Pneumococcal Vaccination
   1. PCV20 and PCV15 were FDA approved for adults 18 and older in 2021 on the basis of improved antibody responses compared with the 13-valent PCV (PCV13).
   2. ACIP pneumococcal vaccine recommendations for patients who have not previously received PCV:
      a. Adults 65 and older should receive one dose of PCV20 alone or one dose of PCV15 followed by one dose of PPSV23 at least 1 year later. Doses do not need to be repeated if given before age 65.
      b. Adults 19–64 years of age with the following underlying conditions should receive one dose of PCV20 alone or one dose of PCV15 followed by one dose of PPSV23 at least 1 year later.
         i. Alcoholism
         ii. Chronic heart disease
         iii. Chronic liver disease
         iv. Chronic lung disease
         v. Cigarette smoking
         vi. Diabetes
         vii. Cochlear implant
         viii. CSF leak
         ix. Congenital or acquired asplenia
         x. Sickle cell disease or other hemoglobinopathies

xi. Patients who are immunocompromised (chronic renal failure, congenital or acquired immunodeficiencies, generalized malignancy, HIV infection, Hodgkin disease, iatrogenic immunosuppression, leukemia, lymphoma, multiple myeloma, nephrotic syndrome, solid organ transplantation)

c. At least 8 weeks between PCV15 and PPSV23 may be considered in adults who are immunocompromised.

3. Adults with previous PPSV23 only may receive PCV20 or PCV15 at least 1 year after their last PPSV23 dose. If PCV15 is used, an additional PPSV23 dose is not needed afterward.
4. Adults with previous PCV13 who have not completed the PPSV23 series should receive 1 dose of PCV20 at least 1 year after their last PCV13 or should complete the PPSV23 series.
5. Figure 4 provides more details for the pneumococcal vaccination recommendations.

E. Influenza Vaccination
1. Egg allergy
   a. Recombinant influenza vaccine (RIV) and cell culture-based inactivated vaccine (ccIIV4) do not contain egg protein.
   b. Patients with a history of severe allergic reaction to egg: If vaccine other than ccIIV4 or RIV is used, vaccinate in a medical setting supervised by a health care provider who is able to recognize and manage severe allergic reactions.
   c. If an adult has experienced only hives after eating eggs or egg-containing foods, the individual can safely receive any available influenza vaccine appropriate for age and health status.
   d. Some people who report egg allergies may not actually be allergic to eggs. Those who can eat a lightly cooked egg (e.g., scrambled egg) without a reaction are likely not allergic and can safely receive any influenza vaccine.
2. Live-attenuated influenza vaccine in adults
   a. Nasal mist
   b. Indicated for those 49 years and younger, except for those:
      i. Who are immunocompromised as the result of any cause (including medications and HIV infection)
      ii. With anatomic or functional asplenia
      iii. With a cochlear implant
      iv. With a cerebrospinal fluid-oropharyngeal communication condition
      v. Close contacts or caregivers of severely immunosuppressed individuals who require a protected environment
      vi. Pregnancy
      vii. Received influenza antiviral medications oseltamivir or zanamivir in the past 48 hours, peramivir in the past 5 days, or baloxavir in the past 17 days
3. If patients have a history of Guillain-Barré syndrome within 6 weeks of a previous dose of influenza vaccine, they should generally not be vaccinated.

F. Herpes Zoster Vaccine
1. Zoster vaccine, recombinant (RZV)
   a. Adults 50 years of age and older and adults 19 years of age and older who are or will be immunocompromised: two-dose regimen at 0 and 2–6 months, minimum 4-week interval
   b. Administer regardless of previous herpes zoster infection or history of zoster vaccine live (ZVL) vaccination
   c. Efficacy close to 90% compared with placebo
   d. Storage
      i. Stored in refrigerator
      ii. Used within 6 hours of reconstitution

G. HPV Vaccine
1. Nine-valent HPV vaccine (9vHPV) is available and may be used for routine HPV vaccination of both females and males.
2. HPV vaccine recently had expanded ages approved for use. It is now approved to be used in males and females 9-45 years of age. HPV vaccination is now recommended as a catch-up vaccine for all people through age 26. For adults 27–45 years of age, shared decision-making is recommended because of lack of widespread public health benefit but recognition that some people may benefit.
3. The series is two doses when started before age 15, with at least 5 months between the two doses. If the series is started at 15 years of age or older or the doses are separated by less than 5 months, the three-dose series (at 0, 1–2, and 6 months) is still recommended.
4. Revaccination with 9vHPV is not recommended if the complete regimen of 2vHPV or 4vHPV has previously been received. The 9vHPV regimen may be completed if started with the 2vHPV or 4vHPV product.

H. COVID-19 Vaccines
1. Four COVID-19 vaccines are available for use: Pfizer-BioNTech, Moderna, Novavax, and Johnson & Johnson/Janssen.
2. An mRNA COVID-19 vaccine series (Pfizer-BioNTech, Moderna) is preferred over Johnson & Johnson/Janssen for both primary series and booster doses due to the rare but serious adverse effect of thrombosis with thrombocytopenia syndrome (TTS).
3. Updated bivalent COVID-19 boosters (Pfizer-BioNTech and Moderna) containing subvariants BA.4 and BA.5 are recommended for individuals age 12 years and older after the primary series.
4. Monovalent vaccine should be used for primary series doses.
5. COVID-19 vaccines may be administered the same day as other vaccines, including influenza.
6. General recommendations for COVID-19 vaccine administration are included in Table 15.

Table 15. Coronavirus Disease 2019 Vaccine Recommendations for Adults Age 18 Years and Older

Patient Population	Vaccine Type[a]						
	Pfizer-BioNTech		Moderna		Novavax		Johnson & Johnson/Janssen
	mRNA		mRNA		Protein subunit		Adenovirus vector
	Doses	Interval[b]	Doses	Interval	Doses	Interval	Considerations
Nonimmunocompromised	Primary series: Monovalent						
	1–2	≥ 3-8 wk	1–2	≥ 4-8 wk	1–2	≥ 3-8 wk	Safety concerns limit use
	Booster dose: Bivalent						
	2–3	≥ 8 wk	2–3	≥ 8 wk	2–3	Moderna or Pfizer-BioNTech ≥ 8 wk	Moderna or Pfizer-BioNTech ≥ 8 wk after previous dose
Immunocompromised	Primary series: Monovalent						
	1–2	≥ 3 wk	1–2	≥ 4 wk	1–2	≥ 3 wk	Safety concerns limit use
	2–3	≥ 4 wk	2–3	≥ 4 wk			
	Booster dose: Bivalent						
	3–4	≥ 8 wk	3–4	≥ 8 wk	2–3	Moderna or Pfizer-BioNTech ≥ 8 wk	Moderna or Pfizer-BioNTech ≥ 8 wk after previous dose

[a]Complete the primary series with the same product if possible.

[b]Consider delaying a primary series or booster dose by 3 months after recent severe acute respiratory syndrome coronavirus 2 infection.

Adapted from: Centers for Disease Control and Prevention (CDC). Interim COVID-19 Immunization Schedule for Ages 6 months and older. Available at www.cdc.gov/vaccines/covid-19/downloads/COVID-19-immunization-schedule-ages-6months-older.pdf.

Patient Cases

8. A 71-year-old woman with COPD is taking tiotropium (Spiriva) inhaled 1 capsule/day. She received the influenza vaccine last October, her last Td vaccine was at age 65, and her PPSV23 was given at age 60. She has not yet received the zoster vaccine, but she had an episode of severe zoster infection 5 years ago. Which is the most appropriate choice of vaccines for the patient's October internal medicine clinic appointment?
   A. Only the influenza vaccine.
   B. Influenza and PCV15 vaccines.
   C. Influenza, PCV15, and RZV.
   D. Influenza, PCV15, RZV, and Tdap.

9. A 20-year-old woman who is going away to college presents for a physical examination in July. She will be living in the dormitory. She smokes 1/2 pack/day but has no other medical conditions. She is up to date on all of her routine childhood vaccines until the age of 9 but has not received any vaccines in the past 11 years. She is not sexually active. Which is the most appropriate choice of vaccines to be given today?
   A. Td and HPV.
   B. Tdap, MenACWY, and HPV.
   C. MenACWY, PCV20, and Td.
   D. MenACWY, PCV20, Tdap, and HPV.

10. A 21-year-old man with type 1 diabetes presents for an influenza vaccine. He has an egg allergy, with angioedema and difficulty breathing after eating eggs. Which is the most appropriate influenza vaccination plan for this patient, assuming all influenza vaccines are available?
   A. IIV, RIV, or live-attenuated influenza vaccine may be used in any setting.
   B. Either IIV or RIV should be used; observe patient for 30 minutes.
   C. RIV or ccIIV should be used.
   D. He should not receive any type of influenza vaccine.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Her symptom frequency of twice weekly, her FEV_1 of more than 80% of predicted (normal), and the lack of interference with activity are consistent with intermittent asthma. Answer A is incorrect; her night awakenings for asthma symptoms occur three times per month, which is consistent with mild persistent asthma. Therefore, Answer B is correct. The specific level of persistent asthma is based on the most severe category met. Answers C and D are incorrect because only one of her signs and symptoms falls under mild persistent asthma (nighttime awakenings), and the rest fall under intermittent asthma.

2. Answer: A

Because she has mild persistent asthma, step 2 is recommended for initial treatment. Answer A is correct given that step 2 treatment involves adding an as-needed low-dose ICS-formoterol. Answer B is incorrect because montelukast is an alternative therapy (not first line) for step 2. Answer C is incorrect; mometasone 220 mcg 2 puffs once daily is a medium-dose ICS (alternative step 3). Budesonide/formoterol at the dose listed is a low-dose ICS plus a LABA (step 3 therapy), making Answer D incorrect.

3. Answer: B

Her asthma is classified as not well controlled because of the frequency of her daytime symptoms and her need to use albuterol more than 2 days/week. When asthma is classified as not well controlled, the recommendation is to increase to the next step of treatment. The patient would now be classified as needing step 3 treatment. The recommended treatment for step 3 is a low-dose ICS-formoterol. Answer A is incorrect because the recommended treatment for step 3 is a daily low-dose ICS plus a LABA. Answer B is correct because it results in single maintenance and reliever therapy (SMART) with ICS-formoterol reliever (step 3 therapy). Adding montelukast is an alternative therapy for step 2 and would not be the preferred option, making Answer C incorrect. Answer D is incorrect; mometasone 220 mcg/puff 2 puffs daily is a medium-dose ICS.

4. Answer: C

Because the patient is experiencing shortness of breath at rest, has trouble with conversation, and has an FEV_1 less than 50% of expected, his asthma exacerbation is classified as severe. For severe asthma exacerbations in the ED setting, pharmacologic treatment is recommended in addition to oxygen to achieve an Sao_2 of 93%–98%; therefore, Answer A is incorrect. Answer B is incorrect because a high-dose inhaled SABA should be combined with ipratropium and administered by either a nebulizer or an MDI with valved holding chamber every 20 minutes for 1 hour or continuously for severe asthma exacerbations in the ED setting. Answer C is correct because it correctly combines a SABA with ipratropium and includes OCSs. Answer D correctly provides a SABA with ipratropium; however, intravenous corticosteroids are not recommended unless the patient has an incomplete response to inhaled and oral treatments.

5. Answer: C

Answer A is incorrect; according to the GOLD guidelines, the recommended treatment for patient group B is the combination of a LABA and LAMA in addition to a SA bronchodilator as needed. Answer B incorrect because it does not include a LAMA in combination with the salmeterol. Answer C correct because the LABA/LAMA combination is recommended for initial treatment of group B. Answer D is incorrect because ICSs are only considered as part of triple therapy (LABA + LAMA + ICS) in group E who have a blood eosinophil count ≥ 300 cells/mcL.

6. Answer: A

This patient is currently being treated with a LAMA (tiotropium). Because her control is worsening with no history of recent exacerbations, she should be placed in the dyspnea pathway of the follow-up treatment algorithm. Because the patient is on bronchodilator monotherapy, her treatment should be intensified, for which combined LA bronchodilators are recommended (LABA plus LAMA). Salmeterol is a LABA; therefore, Answer A is correct. Answer B is incorrect because the long-term use of antibiotics is recommended only in patients on dual bronchodilator therapy who are experiencing exacerbations and are former smokers with an eosinophil count < 100 cells/mcL or patients experiencing

exacerbations on triple therapy who are former smokers. Answers C and D both contain the option of adding fluticasone in some form. Inhaled corticosteroids are recommended only in patients experiencing exacerbations; therefore, Answers C and D are incorrect.

7. Answer: D

Answer A is incorrect because the patient's symptoms indicate that she has a COPD exacerbation and additional treatment is warranted. According to the latest GOLD guidelines, OCSs are indicated in most exacerbations. The recommended dose is oral prednisone 40 mg daily for 5 days. Antibiotic treatment is also indicated because the patient has all three cardinal symptoms of airway infection: increased sputum purulence, increased sputum volume, and increased dyspnea. Azithromycin is one of the recommended antibiotics. Although Answers B and C contain components of the correct treatment for this patient's COPD exacerbation, neither Answer B nor Answer C is complete. Answer D is correct because it incorporates both an OCS and an antibiotic for this patient's COPD exacerbation.

8. Answer: D

The CDC recommends that the influenza vaccine be given every year to every person 6 months and older. All adults 65 and older without a history of PCV should receive PCV20 or PCV15. Adults with previous PPSV23 only may receive PCV20 or PCV15 at least 1 year after their last PPSV23 dose. Recombinant zoster vaccination is recommended in all adults 50 and older, regardless of previous zoster infection. The Tdap vaccine is recommended as a one-time replacement for Td in all people, now including those 65 and older. Answer A is incorrect because it does not address the need for PCV15, zoster vaccine, or Tdap. Answer B is incorrect because it does not address zoster or Tdap vaccination. Answer C is incorrect because it does not include Tdap. Answer D is correct because it includes all four of the appropriate vaccinations for October's visit.

9. Answer: D

First-year college students up to age 21 who live in dormitories, if not previously vaccinated on or after age 16, should receive the meningococcal vaccine (MenACWY; Menactra, Menveo). The PCV20 is recommended for smokers 19–64 years of age, and this patient is a smoker. The Td vaccine should be given every 10 years. In adults younger than 65, a one-time dose of Tdap should be given, regardless of the time interval since the most recent tetanus vaccination. The HPV vaccine is recommended for all people 9–26 years of age. Ideally, it should be given before the start of sexual activity, but it should still be administered to sexually active individuals. Answer A is incorrect because it does not include a meningococcal or pneumococcal vaccine and recommends Td instead of Tdap. Answer B is incorrect because it does not include the pneumococcal vaccine. Answer C is incorrect because it does not include HPV vaccine and recommends Td instead of Tdap. Answer D appropriately includes all four necessary immunizations for the patient's visit today and is correct.

10. Answer: C

Answers A and B are incorrect because of this patient's history of severe allergy to eggs, as indicated by angioedema. If vaccines other than ccIIV4 or RIV are to be used, the individual should be vaccinated in a medical setting supervised by a health care provider who is able to recognize and manage severe allergic reactions. Answer C is correct because in people with a severe egg allergy, ccIIV4 or RIV can be used because they do not contain egg protein. Answer D is incorrect because the patient is still eligible for an influenza vaccine.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Answer A is incorrect because patients with mild intermittent have symptoms 2 days or fewer per week. This patient uses the inhaler throughout the day every day and sometimes at night, indicating that she has daily symptoms. Answer B is incorrect because the patient is having daily symptoms, and patients with mild persistent asthma have symptoms more often than 2 days per week but fewer than daily. Answer C is correct because the patient is having daily symptoms. Answer D is incorrect because "severe persistent" means that the frequency of symptoms is throughout the day, nighttime symptoms often occur seven times a week, a SABA is needed several times a day, normal activity is extremely limited, the FEV_1 is less than 60% of predicted, and the FEV_1/FVC is reduced by more than 5%.

2. Answer: C

Moderate asthma requires step 3 treatment for control. Step 3 preferred treatment is an inhaled steroid (low dose) plus a LABA. Answer A is incorrect because low-dose fluticasone is considered step 2 treatment. Answer B is incorrect because montelukast is an alternative treatment for step 2. Answer C is correct; fluticasone low dose plus salmeterol is the preferred step 3 treatment. Answer D is incorrect because high-dose fluticasone monotherapy is not recommended for treatment of any step of asthma treatment.

3. Answer: D

Answer A is incorrect because nominal data contain no quantitative value and are simply labels. Ordinal data is a measure of non-numeric concepts in which the order of the value is important but the differences between values are not truly known, making Answer B incorrect. Answer C is incorrect because although interval data are ranked in a specific order with a consistent level of magnitude difference between units, there is no absolute zero. Answer D is correct because ratio data are ranked in a specific order with a consistent level of magnitude difference between units, with an absolute zero.

4. Answer: B

The percentage of patients receiving fluticasone/salmeterol who have an asthma-related hospitalization will be compared with the percentage of patients receiving fluticasone who have an asthma-related hospitalization. We assume that these two groups are normally distributed. These data are considered nominal. Use of ANOVA is appropriate when there are more than two treatment groups; therefore, Answer A is incorrect. Answer B is correct because the chi-square test is appropriate for analyzing nominal or categorical data. The Mann-Whitney *U* test is appropriate when continuous data are not normally distributed; therefore, Answer C is incorrect. Answer D is incorrect because the Student unpaired t-test is used for continuous data that are normally distributed.

5. Answer: B

Answer A is incorrect because the influenza vaccine is recommended in people with chronic cardiovascular or pulmonary diseases such as asthma. However, usually the influenza vaccine is given in the fall or early winter to offer protection when the risk of infection is highest. Answer B is correct; the pneumococcal vaccine is recommended in people 19–64 years of age with asthma, and this patient falls into this category. Answer C is incorrect because the tetanus booster (Td) is recommended every 10 years, and it has not been 10 years since this patient's last Td, which was given as Tdap. The herpes zoster vaccine is recommended by the CDC for adults 50 and older so Answer D is incorrect.

6. Answer: B

This patient is in group A, based on having no exacerbations and an mMRC score of 1. A single LA bronchodilator is the best choice of medication treatment. Answer A is incorrect because an ICS is considered only in patient group E with elevated eosinophils and should never be used as monotherapy in COPD. Tiotropium is a LA bronchodilator (anticholinergic) that would be appropriate in this patient, making Answer B correct. (A LABA would also be appropriate, but it was not one of the choices.) Answer C is incorrect because the ICS/LABA combination is generally not preferred for treatment of COPD. Answer D is incorrect because roflumilast is only indicated in severe COPD (FEV1 less than 50% of predicted) associated with chronic bronchitis when the patient has a history of frequent exacerbations.

7. Answer: A

Answer A is correct because dyspnea that is progressive, persistent, and worse with exertion is a hallmark symptom of COPD. Answer B is incorrect because spirometry findings of an FEV_1/FVC less than 70% of predicted are required for a diagnosis of COPD. Answer C is incorrect because although a chronic cough is usually a symptom of COPD, this cough is rarely only nocturnal and is most often present throughout the day. The CAT has a score range of 5–30, with higher scores indicating worse COPD. A CAT score of 5 is within the upper limit of normal scores, making Answer D incorrect.

8. Answer: D

This patient has had two exacerbations in the past year on dual bronchodilator therapy and therefore should follow the exacerbation pathway. The patient is currently taking a LABA/LAMA combination and should be escalated to LABA/LAMA/ICS based on a blood eosinophil count > 100 cells/mcL, making Answer D correct. Answer A is incorrect because this option does not escalate therapy. Answer B is incorrect because roflumilast is considered if a blood eosinophil count is < 100 cells/mcL, FEV_1 is < 50%, and chronic bronchitis is present. Answer C is incorrect because although adding an ICS is appropriate, a single inhaler is preferred because it may be more convenient and effective. In addition, a single ICS inhaler can potentially lead to ICS monotherapy, which is not appropriate in patients with COPD.

9. Answer: D

During each pregnancy, it is recommended that the woman receive a Tdap vaccination, regardless of the time since her last Td or Tdap immunization. Therefore, Answers A and B are incorrect because they do not include Tdap. Answer C is incorrect because an annual influenza vaccine is recommended for all pregnant women, and the visit is taking place in October, when it would be appropriate to administer the influenza vaccine. Answer D is correct because it includes both Tdap and influenza.

10. Answer: A

It is recommended that a one-time dose of Tdap be substituted for Td in all patients and that the HPV vaccine be administered to males up to age 45. Therefore, Answer A is correct. Answer B is incorrect because it is inappropriate to administer the influenza vaccine in July, and the patient has no risk factors indicating that he would benefit from the meningococcal vaccine (e.g., he is not living in a college dormitory and does not travel frequently). Answer C is incorrect because the patient should receive Tdap in place of the Td booster and does not need the meningococcal vaccine. Answer D is incorrect because the patient should receive Tdap in place of the Td booster, and it is not appropriate to administer the influenza vaccine in July.

Pediatrics

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Pediatrics

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Learning Objectives

1. Recommend therapeutic options to target the most common organisms in neonatal and pediatric sepsis and meningitis.
2. Identify the drugs available for preventing and treating respiratory syncytial virus and indications for use.
3. Explain the most common causative organisms of otitis media and potential treatment options.
4. Apply best practice recommendations for pediatric immunizations.
5. Evaluate treatment options for seizures in children, including differences in pharmacokinetics and adverse effects when compared to adults.
6. Implement an appropriate treatment regimen for patients with attention-deficit/hyperactivity disorder.

Abbreviations in This Chapter:

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ADHD	Attention-deficit/hyperactivity disorder
AOM	Acute otitis media
DTaP	Diphtheria, tetanus, and pertussis vaccine
FDA	U.S. Food and Drug Administration
HepB	Hepatitis B
IVIG	Intravenous immunoglobulin
LAIV	Live attenuated influenza vaccine
MMR	Measles, mumps, and rubella
OME	Otitis media with effusion
RSV	Respiratory syncytial virus
RV	Rotavirus
SCD	Sudden cardiac death
Tdap	Tetanus, diphtheria, and pertussis vaccine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 6-year-old boy with a medical history of exercise-induced asthma presents with fever, tachypnea, headache, photophobia, and myalgia. Which organism is most likely to be isolated from this patient?
   A. Respiratory syncytial virus (RSV).
   B. *Streptococcus pneumoniae.*
   C. Group B *Streptococcus.*
   D. *Pseudomonas aeruginosa.*

2. Which is the best assessment of the risk of severe RSV infection and subsequent need for prophylaxis in a 3-month-old girl born at 30 weeks' gestation?
   A. This patient should receive prophylaxis if she is 6 months or younger at the beginning of RSV season.
   B. This patient is at risk only if she has chronic lung disease (i.e., necessitating more than 21% oxygen for at least the first 28 days of life).
   C. All neonates born during RSV season should receive prophylaxis.
   D. This patient should receive prophylaxis only if she has additional risk factors, such as day care attendance or school-aged siblings.

3. Which statement about prophylaxis of bacterial meningitis is the most accurate?
   A. Close contacts of patients with pneumococcal meningitis should receive prophylaxis.
   B. Close contacts of patients with *Haemophilus influenzae* meningitis need prophylaxis only if their immunizations are not up to date.
   C. Rifampin is a first-line agent for prophylaxis against meningococcal meningitis.
   D. Prophylaxis against bacterial meningitis is no longer recommended regardless of the causative organism.

4. A 6-month-old infant who was born at 24 weeks' gestation is brought to the clinic in October for a routine checkup and immunizations. Which is the best recommendation to make for this patient's immunization schedule?
   A. Only two of the five immunizations due should be given at the same time; schedule another appointment for the next week to administer the rest.
   B. Oral polio vaccine should be used to reduce the number of injections needed to complete the schedule.

C. Vaccines should be based on his corrected gestational age rather than on his chronologic age because he was born prematurely.

D. Influenza vaccine should be administered with all other scheduled vaccinations.

5. A physician asks for your recommendation for treating a 5-year-old child with his first case of acute otitis media (AOM). Which statement is the best advice?

A. A blood culture should be obtained to identify the causative organism.

B. Antibiotics might not be warranted at this time.

C. Initiate azithromycin to treat atypical organisms (e.g., mycoplasma).

D. Administer intramuscular ceftriaxone.

6. A 10-year-old female girl with asthma, a history of ventricular septal defect, and attention-deficit/hyperactivity disorder (ADHD) was initially treated with methylphenidate immediate release, but her ADHD symptoms persisted at home and school. Her therapy was then changed to methylphenidate OROS (Concerta). The dose was maximized during the next several weeks; however, her symptoms were still not well controlled throughout the day. She and her family report adherence to the treatment regimen. Which is the best recommendation to make for treating her ADHD?

A. Switch to clonidine extended release.

B. Switch to extended-release mixed amphetamine salts (i.e., Adderall XR).

C. Switch to methylphenidate transdermal system (i.e., Daytrana).

D. Switch to atomoxetine.

7. A 7-year-old child with absence seizures is having breakthrough episodes on ethosuximide. Which is the most appropriate alternative therapy?

A. Valproic acid.

B. Phenytoin.

C. Phenobarbital.

D. Gabapentin.

8. In a retrospective study of the risk of appetite loss in adolescents taking a specific stimulant agent for ADHD management, 7 of 200 patients exposed to the stimulant showed appetite loss, compared with 1 of 198 control subjects (unexposed). Which choice best reflects the correct odds ratio of developing loss of appetite for the case subjects compared with the control subjects?

A. 3.

B. 6.

C. 7.

D. 8.

9. An investigator wants to establish a causal relationship between the use of ceftriaxone in premature neonates and the incidence of kernicterus. Which study design is best to use?

A. Case series.

B. Randomized controlled.

C. Retrospective cohort.

D. Crossover.

10. An 8-month-old infant born at 36 weeks' gestation with hypoplastic left heart disease is admitted during RSV season for stage II (of III) repair of his heart defect. Which statement is most accurate regarding the use of palivizumab for RSV prophylaxis in this patient?

A. He is not at significant risk of severe RSV infection; therefore, palivizumab is not indicated.

B. Palivizumab is indicated to reduce nosocomial transmission of RSV in high-risk patients.

C. Palivizumab is not indicated because he has undergone surgical repair of his heart defect.

D. A dose of palivizumab should be administered postoperatively and continued throughout the RSV season.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Sub-task(s): 1.1.2, 1.1.3, 1.1.6, 1.1.8, 1.1.11, 1.1.14
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Sub-task(s): 1.2.2
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Sub-task(s): 1.3.1, 1.3.2, 1.3.4

2. Application of Evidence to Practice and Education
    a. 2.2. Evaluate pharmacotherapy-related literature and health information. Sub-task(s): 2.2.3

3. Healthcare Systems and Population Health
    a. 3.3. Incorporate public health initiatives to improve population health. Sub-task(s): 3.3.1

I. SEPSIS AND MENINGITIS

A. Clinical Presentation
1. Signs and symptoms
   a. Neonates (less than 28 days old or less than 44 weeks' corrected gestational age for premature neonates who were originally born less than 37 weeks' gestational age)
      i. General: Temperature instability, feeding intolerance, lethargy, grunting, nasal flaring, retractions, apnea
      ii. More likely to be associated with meningitis: Bulging fontanelle and seizures
   b. Infants (1–12 months) and children (1–18 years)
      i. General: Fever, loss of appetite, emesis, myalgias, arthralgias, cutaneous manifestations (e.g., petechiae, purpura, rash)
      ii. More likely to be associated with meningitis: Nuchal rigidity, back pain, Kernig sign (restriction in passive extension at the knee because of spasm of the hamstring muscles), Brudzinski sign (consists of reflex flexion of a lower extremity after passive flexion of the opposite extremity), headache, photophobia, altered mental status, and seizures
2. Early versus late onset neonatal sepsis
   a. Onset
      i. Early: Within 72 hours of birth
      ii. Late: After the first 72 hours of life
   b. Risk factors
      i. Early
         (a) Usually related to maternal or obstetric risk factors: very low birth weight (less than 1500 g), prolonged rupture of amniotic membranes (greater than 18 hours), maternal fever, prolonged labor, maternal genitourinary tract colonization with group B *Streptococcus*, maternal endometritis, or chorioamnionitis
      ii. Late
         (a) Unrelated to obstetric risk factors
         (b) Usually related to iatrogenic/nosocomial factors (e.g., endotracheal tubes, central venous catheters)
   c. Incidence
      i. Early
         (a) Incidence increases with decreasing gestational age:
            (1) 0.5 of 1000 live births (term neonates)
            (2) 1 of 1000 live births (late preterm neonates 34–36 weeks' gestation)
            (3) 6 of 1000 live births (preterm neonates less than 34 weeks' gestation)
            (4) 20 of 1000 live births (preterm neonates less than 29 weeks' gestation)
            (5) 32 of 1000 live births (preterm neonates 22–24 weeks' gestation)
         (b) Meningitis occurs in less than 10% of cases.
      ii. Late
         (a) Incidence increases with decreasing gestational age:
            (1) 9% greater than 34 weeks' gestation
            (2) 56% 24–25 weeks' gestation
         (b) Meningitis occurs in 60% of cases

d. Mortality
    i. Increases with decreasing gestational age
        (a) 1.6% in term neonates born 37 weeks' gestation or greater
        (b) 30% in preterm neonates 25–28 weeks
        (c) 50% in preterm neonates 22–24 weeks

3. Definition of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in children
    a. SIRS: Presence of at least two of the four following criteria, one of which must be abnormal temperature or leukocyte count:
        i. Core temperature greater than 38.5°C or less than 36°C
        ii. Tachycardia (value based on age) over a 1/2- to 4-hour period or for infants younger than 1 year: bradycardia (value based on age) over a 1/2-hour period
        iii. Tachypnea (value based on age)
        iv. Leukocyte count elevated or depressed for age or greater than 10% immature neutrophils
    b. Sepsis: SIRS in the presence of, or as a result of, suspected or proven infection
    c. Severe sepsis: Sepsis plus one of the following:
        i. Cardiovascular organ dysfunction
        ii. Acute respiratory distress syndrome
        iii. Two or more other organ dysfunctions
    d. Septic shock: Sepsis and cardiovascular organ dysfunction, defined as one of the following despite administration of a fluid bolus of 40 mL/kg or greater in 1 hour:
        i. Decrease in blood pressure to less than 5th percentile on the basis of age or systolic blood pressure less than 2 SD on the basis of age
        ii. Need for vasoactive medications to maintain blood pressure
        iii. Two of the following:
            (a) Unexplained metabolic acidosis
            (b) Increased lactate
            (c) Oliguria (urinary output less than 0.5 mL/kg/hour)
            (d) Prolonged capillary refill greater than 5 seconds
            (e) Core to peripheral temperature gap greater than 3°C

4. Cerebrospinal fluid findings (Table 1)

Table 1. Cerebrospinal Fluid Findings

Laboratory Value	Normal Child	Normal Newborn	Bacterial Meningitis	Viral Meningitis
WBC (cells/mL)	0–6	0–30	>1000	100–500
Neutrophils (%)	0	2–3	>50	<40
Glucose (mg/dL)	40–80	32–121	<30	>30
Protein (mg/dL)	20–30	19–149	>100	50–100
RBC (cells/mL)	0–2	0–2	0–10	0–2

RBC = red blood cell count; WBC = white blood cell count.

Adapted with permission from the American Academy of Pediatrics: Wubbel L, McCracken GH. Management of bacterial meningitis: 1998. Pediatr Rev 1998;19:78-84.

Patient Case

1. An infant born at 36 weeks' gestation develops respiratory distress, hypotension, and mottling at 5 hours of life. The child is transported to the neonatal intensive care unit, where he has a witnessed seizure, and cultures are obtained. Maternal vaginal cultures are positive for group B *Streptococcus*, and three doses of penicillin were given to the mother before delivery. Which is the best empiric antibiotic regimen?
   A. Vancomycin plus cefotaxime.
   B. Ampicillin plus ceftazidime.
   C. Ampicillin plus ceftriaxone.
   D. Ceftazidime plus gentamicin.

B. Common Pathogens for Sepsis and Meningitis (Table 2)

Table 2. Common Pathogens

Age	Organism[a]
0–1 mo	Early onset: Group B *Streptococcus* (*Streptococcus agalactiae*) – 40%–45% of cases in term and late-preterm neonates (20% of cases in preterm neonates < 34 weeks' gestation) *Escherichia coli* – 10%–15% of cases in term and late-preterm neonates (50% of cases in preterm neonates < 34 weeks' gestation) *Listeria monocytogenes* – < 2% of cases in term and late-preterm neonates Late onset: Viral (e.g., herpes simplex virus) Coagulase-negative *Staphylococcus* (nosocomial) Gram-negative bacteria (e.g., *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter* spp.; nosocomial)
1–3 mo	Neonatal pathogens (see above), Group B *Streptococcus* - 39% of cases *Haemophilus influenzae* type B[b] *Neisseria meningitidis* - 12% of cases *Streptococcus pneumoniae* - 14% of cases
3 mo – 12 yr	*Haemophilus influenzae* type B[b] *Neisseria meningitidis* - 34%–55% of cases *Streptococcus pneumoniae* - 24%–45% of cases
> 12 yr	*Neisseria meningitidis* - 55% of cases *Streptococcus pneumoniae* - 21% of cases

[a]For healthcare-associated meningitis and ventriculitis, organisms will vary and are likely to include more resistant organisms.

[b]*H. influenzae* is no longer a common pathogen where the vaccine is routinely used.

C. Potential Empiric Antibiotic Regimens for Sepsis and Meningitis (Table 3)

Table 3. Potential Empiric Antibiotic Regimens

Age	Regimen
0–1 mo	Ampicillin + gentamicin[a]
1–3 mo	Ampicillin + ceftriaxone[b] or vancomycin[c] + ceftriaxone[b]
>3 mo	Ceftriaxone + vancomycin[cd]

[a]May consider use of broader-spectrum gram-negative agents in very critically ill neonates depending on local antibiotic resistance data. Cefotaxime (or ceftazidime with cefotaxime drug shortage) may be considered instead of gentamicin when there is a concern for meningitis.

[b]May consider cefotaxime (or ceftazidime with cefotaxime drug shortage) instead of ceftriaxone for infants < 2 mo because of potential contraindications with ceftriaxone.

[c]May defer vancomycin if no concern for meningitis.

[d]For healthcare-associated meningitis and ventriculitis, the empiric regimen should be vancomycin + an antipseudomonal beta-lactam.

Patient Cases

2. Culture results for the patient in question 1 reveal gram-negative rods in the cerebrospinal fluid. Which recommendation regarding antibiotic prophylaxis is best?
   A. The patient's 5-month-old stepsister is at high risk because she is not fully immunized; therefore, the patient should receive rifampin.
   B. The patient should receive rifampin to eliminate nasal carriage of the pathogen.
   C. Antibiotic prophylaxis is not indicated in this case.
   D. All close contacts should receive rifampin for prophylaxis.

3. A 6-year-old boy presents to the emergency department with a temperature of 104°F (40°C), altered mental status, and petechiae. There is no history of trauma. The results of a toxicology screen are negative. A complete blood cell count reveals 32×10^3 cells/mm^3 with 20% bands. Culture results are pending. The patient has no known drug allergies. Which antibiotic regimen provides the best empiric coverage?
   A. Ampicillin plus gentamicin.
   B. Cefuroxime.
   C. Ceftriaxone plus vancomycin.
   D. Rifampin.

D. Sequelae of Meningitis
   1. Hearing loss
   2. Mental retardation and learning deficits
   3. Visual impairment
   4. Seizures
   5. Hydrocephalus
   6. Mortality 5%–10% (10%–20% in neonates)

E. Steroids for Meningitis
   1. Use of steroids for pediatric meningitis to prevent neurologic complications (e.g., hearing loss) is controversial.
   2 A large meta-analysis showed reduced hearing loss with *H. influenzae* type B (Hib) meningitis only in children. However, Hib is less common now with routine vaccination.
   3. Recommendations from the American Academy of Pediatrics (AAP) on this topic are summarized as follows:
      a. Dexamethasone may be considered for suspected bacterial meningitis caused by Hib in children older than 6 weeks after considering risk-benefit.
         i. Example: A child with signs/symptoms of meningitis has confirmed recent exposure to someone with a Hib infection
      b. Data are insufficient to recommend routine adjunctive corticosteroid therapy for pediatric pneumococcal meningitis.
      c. If dexamethasone is used, it should be administered before or at the same time as the first dose of antibiotics.
      d. The usual dosage is dexamethasone 0.15 mg/kg/dose every 6 hours for 2 days.

F. Chemoprophylaxis of Bacterial Meningitis
   1. Purpose: Prevent the spread of *H. influenzae* and *N. meningitidis* to contacts of the patient at high risk
   2. High-risk groups
      a. Household contacts
      b. Nursery or day care center contacts
      c. Direct contact (e.g., health care providers) with index patient's secretions during the 7 days preceding or up to 24 hours after initiation of appropriate antibiotic therapy
      d. Individuals with prolonged contact (more than 8 hours for N. meningitidis and 4 hours or more for H. influenzae) while close (less than 3 feet) to patient in the preceding 7 days of symptom onset
   3. Regimens (Table 4)

Table 4. Regimens for Chemoprophylaxis[a]

Drug	*Neisseria meningitidis*	*Haemophilus influenzae*
Rifampin	<1 mo old: 5 mg/kg/dose PO every 12 hr × 2 days ≥1 mo old: 10 mg/kg/dose (maximum 600 mg) PO every 12 hr × 2 days	<1 mo old: 10 mg/kg/dose PO daily × 4 days ≥ 1 mo old: 20 mg/kg/dose (maximum 600 mg) PO daily × 4 days
Ceftriaxone	<15 yr old: 125 mg IM × 1 dose ≥15 yr old: 250 mg IM × 1 dose	Not indicated
Ciprofloxacin[b]	≥1 mo old: 20 mg/kg/dose (maximum 500 mg) PO × 1 dose	

[a]Azithromycin is a possible alternative, but it is not routinely recommended.

[b]Ciprofloxacin should only be used if fluoroquinolone-resistant strains of *N. meningitidis* have not been reported in the community.

IM = intramuscularly; PO = orally/enterally.

II. RSV INFECTION

A. Clinical Presentation
   1. Seasonal occurrence: Depends on geographic location and usually lasts 4–5 months
      a. Season onset ranges from October to late January
      b. Season offset ranges from late January to early April
      c. Exception: Florida has an earlier RSV season onset and longer duration than the rest of the country
      d. Exception: There was an unusual spike in RSV cases in summer/fall 2021 during the coronavirus disease 2019 (COVID-19) pandemic after nearly no cases during winter 2020–2021
   2. Signs and symptoms
      a. Neonates and infants: Lower respiratory tract symptoms (e.g., bronchiolitis and pneumonia), wheezing, lethargy, fever, irritability, poor feeding, and apnea
      b. Older children: Upper respiratory tract symptoms (e.g., rhinorrhea, cough)
      c. Most cases are mild and self-limited.
   3. RSV accounts for more than 80% of lower respiratory tract infections in infants younger than 1 year.
   4. RSV is the most common cause of pediatric bronchiolitis and pneumonia.

B. Risk Factors for Severe Disease
   1. Premature birth
   2. Chronic lung disease or bronchopulmonary dysplasia
   3. Cyanotic or complicated congenital heart disease
   4. Moderate to severe pulmonary hypertension
   5. Immunodeficiency
   6. Airway abnormalities or neuromuscular conditions compromising the handling of respiratory secretions
   7. Other
      a. Lower socioeconomic status
      b. Passive smoking
      c. Day care attendance
      d. Siblings younger than 5 years

Patient Case

4. You are screening infants during the current RSV season for risk factors associated with the development of severe RSV infection. Which patient is the best candidate for the use of palivizumab for RSV prophylaxis?

   A. An 18-month-old child, born at 26-weeks' gestation with a history of chronic lung disease who has not received oxygen or medications during the past 8 months.

   B. A 5-month-old infant, born at 28-weeks' gestation with a history of chronic lung disease who was discharged from the hospital without oxygen or medications.

   C. A 41-day-old infant, born at 31 weeks' gestation, without a history of chronic lung disease who will attend day care.

   D. A 10-month-old infant, born at 37 weeks' gestation, with a surgically repaired congenital heart defect.

C. Prophylaxis
   1. Nonpharmacologic: Avoid crowds during RSV season and conscientiously use good handwashing practice
   2. Palivizumab (Synagis®)
      a. Dosing: 15 mg/kg/dose intramuscularly, given monthly during RSV season for up to 5 doses
         i. There is a 58% decrease in palivizumab serum concentration after cardiopulmonary bypass; therefore, an additional postoperative dose of palivizumab is recommended as soon as the patient is medically stable.
      b. Effects on outcomes
         i. A 55% reduction in hospitalizations for RSV
         ii. No reduction in overall mortality
         iii. Does not interfere with the response to vaccines
         iv. Not recommended for the prevention of nosocomial transmission of RSV
      c. The AAP recommendations for use were most recently updated in 2014 and were reaffirmed in 2017 and again in 2019 (Table 5).
      d. Note that prophylaxis should be discontinued if an RSV hospitalization occurs.
      e. AAP issued updated interim guidance in 2021 and again in 2022 addressing the change in RSV circulation and interseasonal spread that occurred during the COVID-19 pandemic. AAP strongly supports consideration of palivizumab for eligible patients also during the interseasonal spread of RSV and notes that use should not be limited only to the typical fall/winter season when interseasonal RSV cases are high.
   3. Other monoclonal antibodies and vaccines are in development; however, palivizumab is currently the only U.S. Food and Drug Administration (FDA)-approved product recommended for RSV prevention.

Table 5. AAP Guidelines for Palivizumab Use

Gestational Age (wk + days)	Age at Start of RSV Season (mo)	Other Required Criteria	Maximum Number of Doses
<29 + 0	<12	—	5
29 + 0 to 31+6	<12	Chronic lung disease necessitating more than 21% oxygen for at least the first 28 days of life	5
<32 + 0	<24	Consider prophylaxis for a second RSV season if chronic lung disease has necessitated medical therapy within the 6 months preceding the start of RSV season	5
Any	<12	Patient with hemodynamically significant acyanotic[a] congenital heart disease receiving medication for congestive heart failure *and* will need cardiac surgery	5
Any	<12	Moderate to severe pulmonary hypertension	5
Any	<12	Congenital abnormalities of airway or neuromuscular disease that impairs the ability to clear airway secretions	5
Any	<24	Profoundly immunocompromised (may be considered)	5

[a]Infants with cyanotic heart defects can be considered for prophylaxis after consultation with a pediatric cardiologist.

AAP = American Academy of Pediatrics; RSV = respiratory syncytial virus.

Patient Case

5. An 18-month-old child with a history of premature birth and chronic lung disease is admitted to the pediatric intensive care unit with fever, respiratory distress necessitating intubation, and a 3-day history of coldlike symptoms. The results of a nasal swab are positive for RSV. Which is the best intervention?
   A. Palivizumab.
   B. Dexamethasone.
   C. Cefuroxime.
   D. Supportive care.

D. Treatment
   1. Supportive care
      a. Hydration
      b. Supplemental oxygen
      c. Mechanical ventilation as needed
      d. Analgesics for fever
   2. Ribavirin
      a. Active against RSV replication
      b. Not shown to reduce mortality in immunocompetent patients
      c. Not shown to reduce ventilator days, stay in the intensive care unit or hospital, or hospital cost
      d. The AAP states that oral ribavirin "may be considered" in a select group of high-risk patients (e.g., those with complicated congenital heart disease, chronic lung disease or bronchopulmonary dysplasia, immunocompromised) but that "routine use is not recommended."

3. Inhaled β_2-agonists, racemic epinephrine
    a. Not shown to improve outcome measures
    b. Some practitioners may give a trial of these therapies, but this is not considered the standard of care, nor is it recommended by the current AAP guideline.
4. Corticosteroids
    a. Not shown to improve outcome measures
    b. Use is not recommended.
5. Inhaled hypertonic saline
    a. Should not be administered in the emergency department
    b. May be considered for hospitalized patients; however, the evidence supporting use is weak.
6. Antibiotics: Not indicated unless secondary bacterial infection develops

III. OTITIS MEDIA

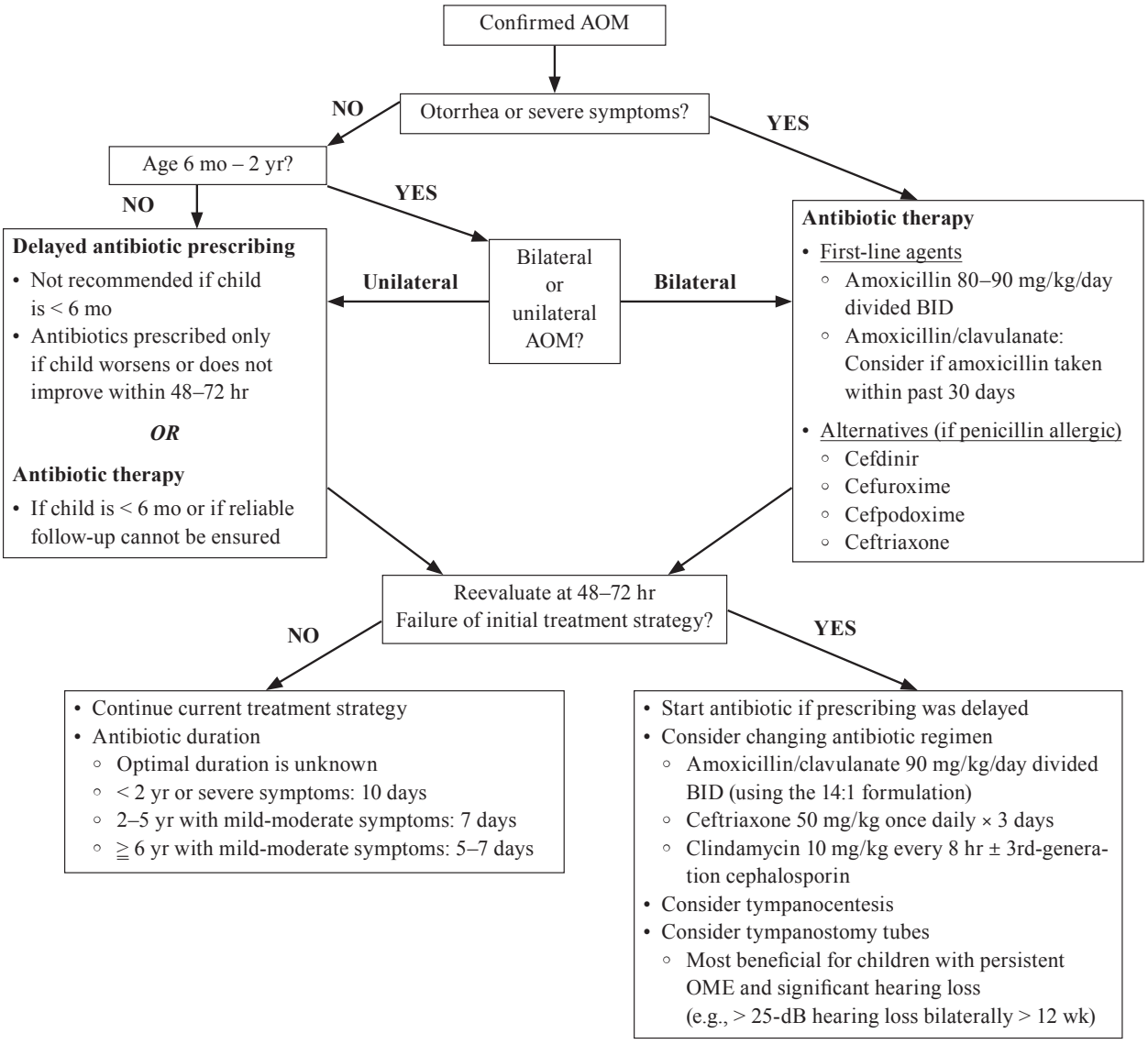
A. Clinical Presentation
    1. Definitions
        a. Acute otitis media: Presence of middle ear effusion and evidence of middle ear inflammation
            i. Middle ear effusion may be indicated by bulging tympanic membrane, decreased or no mobility of the tympanic membrane, purulent fluid in the middle ear.
            ii. Inflammation of the middle ear may be indicated by erythema of the tympanic membrane or otalgia.
        b. Otitis media with effusion (OME): Fluid in the middle ear without evidence of local or systemic illness
        c. Recurrent AOM: Three or more episodes of acute otitis within 6 months or four episodes within 1 year with at least 1 episode within the most recent 6 months
    2. Risk factors
        a. Younger age (generally less than school age)
        b. Day care attendance
        c. Absence of breastfeeding
        d. Family history of AOM
        e. Positioning during feeding (e.g., supine position during bottle-feeding allows reflux into Eustachian tubes)
        f. Lower socioeconomic status
        g. Smokers in the household
        h. Craniofacial abnormalities or cleft palate
        i. Lack of pneumococcal conjugate vaccine and influenza vaccine administration
        j. Immune deficiencies
        k. Cochlear implants
        l. Siblings in the home
        m. Seasonal cooler months (winter)
    3. Incidence
        a. AOM in first year of life: 25%
        b. AOM by 5 years of life: 60%
        c. Peak incidence at 6 to 12 months of age

B. Common Pathogens
   1. Viral
   2. *Streptococcus pneumoniae*
   3. Nontypeable *H. influenzae*
   4. *Moraxella catarrhalis*

C. Signs & Symptoms:
   1. Otorrhea
   2. Erythema
   3. Tugging or pulling of ears (otalgia)
   4. Fever
   5. Irritability/sleep changes

D. Treatment
   1. General principles
      a. Clinical resolution will occur in a significant number of cases without antibiotic therapy.
      b. Immediate antibiotic therapy is warranted for AOM with bulging tympanic membrane, perforation, or otorrhea.
      c. Delayed antibiotic prescribing (i.e., treatment only if symptoms are severe: otalgia persists for more than 48–72 hours or temperature greater than 102.2°F [39°C] in the past 48 hours) is an acceptable strategy in children older than 2 years with AOM without severe systemic symptoms.
         i. Analgesics (e.g., ibuprofen, acetaminophen) are more beneficial than antibiotics for relieving otalgia within the first 24 hours and are recommended regardless of antibiotic use.
            (a) Ibuprofen 5–10 mg/kg every 6–8 hours (not recommended if less than 6 months old)
            (b) Acetaminophen 10–15 mg/kg every 4–6 hours
         ii. Antibiotics also can be deferred in otherwise healthy children between 6 months and 2 years of age if their symptoms are mild and otitis media is unilateral (as opposed to bilateral).
         iii. Caregiver must be reliable to recognize worsening of condition and gain immediate access to medical care, if needed.
         iv. Not recommended for infants younger than 6 months
      d. Persistence of middle ear fluid is likely after treatment for AOM and does not warrant repeated treatment.
         i. 50% persistent OME after 1 month
         ii. 20% persistent OME after 2 months
         iii. 10% persistent OME after 3 months
      e. Antibiotics are not generally warranted for OME because of the high rate of spontaneous resolution.
         i. Antibiotics are recommended only if bilateral effusions persist for more than 3 months.
         ii. Corticosteroids, antihistamines, and decongestants are not recommended.

2. Suggested treatment algorithm (Figure 1)


Confirmed AOM
Otorrhea or severe symptoms?
NO
YES
Age 6 mo – 2 yr?
NO
YES
Delayed antibiotic prescribing
• Not recommended if child is < 6 mo
• Antibiotics prescribed only if child worsens or does not improve within 48–72 hr
OR
Antibiotic therapy
• If child is < 6 mo or if reliable follow-up cannot be ensured
Unilateral
Bilateral or unilateral AOM?
Bilateral
Antibiotic therapy
• First-line agents
◦ Amoxicillin 80–90 mg/kg/day divided BID
◦ Amoxicillin/clavulanate: Consider if amoxicillin taken within past 30 days
• Alternatives (if penicillin allergic)
◦ Cefdinir
◦ Cefuroxime
◦ Cefpodoxime
◦ Ceftriaxone
Reevaluate at 48–72 hr
Failure of initial treatment strategy?
NO
YES
• Continue current treatment strategy
• Antibiotic duration
◦ Optimal duration is unknown
◦ < 2 yr or severe symptoms: 10 days
◦ 2–5 yr with mild-moderate symptoms: 7 days
◦ ≧ 6 yr with mild-moderate symptoms: 5–7 days
• Start antibiotic if prescribing was delayed
• Consider changing antibiotic regimen
◦ Amoxicillin/clavulanate 90 mg/kg/day divided BID (using the 14:1 formulation)
◦ Ceftriaxone 50 mg/kg once daily × 3 days
◦ Clindamycin 10 mg/kg every 8 hr ± 3rd-generation cephalosporin
• Consider tympanocentesis
• Consider tympanostomy tubes
◦ Most beneficial for children with persistent OME and significant hearing loss (e.g., > 25-dB hearing loss bilaterally > 12 wk)

BID = twice daily; OME = Otitis media with effusion.

Figure 1. Suggested treatment algorithm for acute otitis media (AOM).

E. Complications of AOM: Incompletely treated or untreated:
   1. Hearing loss
   2. Mastoiditis
   3 Tympanic membrane perforation
   4. Otorrhea

F. Prevention Strategies
   1. Antibiotic prophylaxis
      a. Reduces occurrence by about one episode per year
      b. The risk of promoting bacterial resistance may outweigh the slight benefit.
      c. AAP recommends against routine use for children with recurrent AOM.
   2. Immunization: Pneumococcal and influenza vaccines should be administered according to the AAP and Advisory Committee on Immunization Practices (ACIP) recommendations.
   3. Modification of risk factors

Patient Cases

6. A 5-month-old infant who was born at term and is otherwise healthy was treated for her first case of otitis media with amoxicillin 45 mg/kg/day for 7 days. On follow-up examination, her pediatrician noticed fullness in the middle ear and a cloudy tympanic membrane with decreased mobility. She is now afebrile and eating well. Which is the best recommendation for her treatment?
   A. No antibiotics at this time.
   B. High-dose (90 mg/kg/day) amoxicillin for 7 days.
   C. Decongestant and antihistamine daily until resolution.
   D. Azithromycin.

7. A 4-year-old boy receives a diagnosis of his fourth case of otitis media within 12 months. He has not shown evidence of hearing loss or delay in language skills. Which is the best intervention at this point?
   A. Giving long-term antibiotic prophylaxis.
   B. Inserting tympanostomy tubes.
   C. Administering high-dose amoxicillin and ensuring that he is up to date on his pneumococcal and influenza vaccines.
   D. No antibiotic therapy is warranted.

IV. IMMUNIZATIONS

A. Recommended Schedule (Figure 2)
   1. Some major changes and several clarifications have been made to the routine childhood schedule in the last 10 years.
      a. Replacement of 7-valent conjugated pneumococcal vaccine with 13-valent conjugated pneumococcal vaccine (PCV13, Prevnar 13) for all children younger than 6 years
      b. Human papillomavirus vaccine (HPV4, Gardasil) received an FDA label-approved indication in males and females aged 9–26 years for prevention of genital warts and females aged 9–26 years for the prevention of cervical, vulvar, vaginal, and anal cancer. It is now recommended for routine vaccination of adolescent males and females.
      c. Live attenuated influenza vaccine (LAIV) was previously not recommended during the 2016-2017 and 2017-2018 influenza seasons. It was, however, considered an option again starting with the 2018-2019 season in patients to whom influenza injection would otherwise not be given. Use of LAIV must be assessed annually. LAIV should not be used in children younger than 2 years or children 2–4 years of age with a diagnosis of asthma in the preceding year. Caution should be used in children older than 5 years with asthma.
      d. Hepatitis B (HepB) vaccine for the birth dose should be given within 24 hours of birth added to footnote of 2017 update.

e. For children and adolescents who have a delayed start to immunizations, a catch-up schedule exists.
f. A new figure for vaccines that might be indicated for children and adolescents aged 18 years or younger based on medical indications was added.
    i. Most children with medical conditions can (and should) be vaccinated according to the routine schedule.
    ii. It provides details for when a medical condition is a contraindication or precaution to vaccination.
    iii. It indicates when additional doses of vaccination may be required because of a medical condition.
g. Refer to the National Immunization Program Web site (www.cdc.gov/vaccines).
h. New formulations of licensed influenza vaccines with a volume of 0.5 mL per dose were approved for children 6–36 months of age in 2019. Children 6–35 months of age may now receive either the 0.25-mL or the 0.5-mL dose, with no preference, and children 36 months and older continue to receive a 0.5-mL dose.
i. The first vaccine indicated for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was approved in August 2021 for individuals 16 years of age and older. Additional vaccine approvals have been provided by emergency use authorization for children as young as 6 months, at the time when this chapter was written. CDC has provided an interim COVID-19 immunization schedule for children separate from the general child and adolescent immunization schedule. This COVID-19 immunization schedule is updated regularly as approvals and indications change. For the most up-to-date schedule, refer to the CDC website.

Patient Case

8. A 1-year-old boy with a history of Kawasaki disease treated 4 months ago with intravenous immunoglobulin (IVIG) is being seen by his pediatrician for a well-child checkup. He is due for the measles, mumps, and rubella (MMR) and varicella vaccines. He has no known drug allergies, but he has many food allergies, including peanuts and eggs. His mother has several concerns about administering these vaccines. Which concern is the best reason to defer administering vaccines in this patient?

    A. Association between MMR vaccine administration and the development of autism.

    B. Allergic reaction after MMR administration in a patient with an egg allergy.

    C. Many concurrent vaccines can overload the patient's immune system.

    D. Decreased vaccine efficacy because of previous IVIG administration.

2. Combination vaccines
    a. Main advantage: Reduction in the number of injections needed to complete recommended schedule
    b. The FDA mandates that the safety and efficacy of combination products not be less than those of the individual components.
    c. The MMR and varicella combination vaccine (ProQuad)
        i. Research from the Centers for Disease Control and Prevention and manufacturer indicated a higher incidence of febrile seizures in children 12–23 months of age who received the combination product compared with those who received the separate MMR and varicella vaccines.
        ii. Since June 2009, ACIP has expressed a preference for separate MMR and varicella vaccines as the first dose given to children 12–47 months of age. The combination product can be used for the second dose at any age and for the first dose in children age 48 months or older.
    d. Adding HepB to combination products can result in an extra dose being provided (e.g., monovalent HepB given at birth and then combination products at 2, 4, and 6 months); however, ACIP states that this is a safe practice.

3. Interchangeability of products
    a. ACIP recommends that the same product be used throughout the primary series; however, if the previous product's identity is not known or is no longer available, any product may be used.
    b. For diphtheria, tetanus, and pertussis vaccine (DTaP): The current standard of care is to use the same product for at least the first three doses of the five-dose series; however, if the product used previously is not known or is unavailable, any product can be used.
    c. For tetanus, diphtheria, and pertussis vaccine (Tdap): Boostrix or Adacel can be used for the booster dose, regardless of the manufacturer of the DTaP product administered during the primary immunization series.
    d. For HepB: It is acceptable to use Engerix-B and Recombivax HB interchangeably. Children and adolescents 11–15 years of age can receive a two-dose series with Recombivax HB only, whereas Engerix-B would still be a three-dose series. Heplisav-B should only be used in patients 18 years or older.
    e. For polio: Oral polio vaccine and inactivated poliovirus vaccine provide equivalent protection against paralytic poliomyelitis; however, because the only cases of polio in the United States since 1979 have been vaccine associated (i.e., from the live virus in oral polio vaccine), oral polio vaccine is no longer recommended.
    f. For Hib: These products can be used interchangeably; however, if the regimen is completed using PedvaxHIB exclusively, only three doses are needed for routine immunization; regimens using Hiberix, ActHIB, Pentacel, or Vaxelis should include four doses even if the regimen is completed using PedvaxHIB. Vaxelis is not recommended as a booster dose.
    g. For Rotavirus (RV): These products can be used interchangeably; however, if the regimen is completed using Rotarix exclusively, only two doses are needed; regimens using RotaTeq or when the product is unknown should include three doses.

B. Barriers to Routine Immunization
    1. Contraindications
        a. Anaphylactic reaction to vaccine or any of its components
            i. Inactivated poliovirus vaccine, MMR, and varicella contain neomycin.
            ii. Egg allergy is not considered a contraindication to any form of influenza vaccine. LAIV was approved for use in patients with egg allergy in 2016. Additionally, ACIP evaluated 3 studies looking at use of LAIV in egg-allergic children, and no cases of anaphylaxis occurred.
            iii. Severe egg allergy is not considered a contraindication to MMR, which is grown in chick embryo tissue.
        b. Acute moderate to severe febrile illness
        c. Immunodeficiency: Oral polio vaccine, MMR, varicella
        d. Pregnancy: MMR, varicella
        e. Recent administration of immune globulin: MMR, varicella
            i. Delay administration of vaccine product.
            ii. Interval between immune globulin dose and administration of vaccine depends on indication for and dose of immune globulin.
        f. Encephalopathy within 7 days after administration of a previous dose of DTaP
        g. History of intussusception: Rotavirus vaccine
    2. Misconceptions about contraindications (i.e., these are *not* contraindications)
        a. Mild acute illness
        b. Current antimicrobial therapy
        c. Reaction to DTaP involving only soreness, redness, or swelling at the site
        d. Pregnancy of the mother of the vaccine recipient
        e. Breastfeeding

f. Allergies to antibiotics other than neomycin or streptomycin
g. Family history of an adverse effect after vaccine administration

3. Other factors associated with under-immunization
   a. Low socioeconomic status
   b. Late start of vaccination series
   c. Missed opportunities
      i. Provider unaware that vaccination is due
      ii. Failure to provide simultaneous vaccines
      iii. Inappropriate contraindications (see previous discussion)
   d. Concern about potential adverse reactions
      i. Autism: The association with MMR vaccine has not been proven.
      ii. Guillain-Barré syndrome: The association with meningococcal conjugate vaccine has not been proven.
         (a) Fifteen reported cases in adolescents after receiving meningococcal vaccine
         (b) ACIP continues to recommend the routine use of meningococcal vaccine.
      iii. Intussusception: An association with RV vaccine led to the market withdrawal of one particular brand of RV vaccine (RotaShield); two products are currently available.
         (a) Live, oral human-bovine reassortant rotavirus vaccine (RotaTeq, licensed in 2006)
         (b) Live, attenuated human rotavirus vaccine (Rotarix, licensed in 2008)
         (c) Neither product has been associated with intussusception.
      iv. Safety concerns about any vaccine product should be reported through the Vaccine Adverse Events Reporting System.
   e. Belief that vaccine-preventable diseases no longer pose a significant health risk
   f. Belief that too many vaccines all at once can overwhelm the immune system and make the child sick
   g. Religious or philosophical beliefs that oppose vaccinations

Patient Case

9. The following patients are seeing their pediatrician today and are due for immunizations according to the routine schedule. For which patient would it be best to recommend deferring immunizations until later?

   A. A 12-month-old boy who recently completed a cycle of chemotherapy for acute lymphocytic leukemia.

   B. A 6-month-old girl receiving amoxicillin for otitis media.

   C. A 12-month-old HIV-positive boy whose most recent CD4 count was greater than 1000.

   D. A 12-year-old girl completing a prednisone "burst" (1 mg/kg/day for 5 days) for asthma exacerbation.

C. Considerations in Special Populations (Figure 2)
   1. Preterm infants
      a. Immunize according to chronologic age, as opposed to corrected gestational age
      b. Do not lower vaccine doses
      c. If birth weight is less than 2 kg, delay HepB vaccine because of reduced immune response until the patient is 1 month old or at hospital discharge if it occurs before 1 month of age (unless the mother is positive for HepB surface antigen, in which case the newborn should receive HepB vaccine regardless of birth weight). Newborns to mothers with Hepatitis B should also receive Hepatitis B immune globulin.
   2. Children who are immunocompromised
      a. Should not receive live vaccines (e.g., MMR, varicella, rotavirus, LAIV, yellow fever, and oral typhoid)
      b. Inactivated vaccines and immune globulins are appropriate.

   c. Household contacts should not receive oral polio vaccine; however, MMR, influenza, varicella, and rotavirus vaccines are recommended.
3. Patients receiving corticosteroids
   a. Live vaccines can be administered to patients receiving the following:
      i. Topical corticosteroids
      ii. Physiologic maintenance doses
      iii. Low or moderate doses (less than 2 mg/kg/day of prednisone equivalent)
   b. Live vaccines can be given immediately after discontinuation of high doses (2 mg/kg/day or more of prednisone equivalent) of systemic steroids given for less than 14 days.
   c. Live vaccines should be delayed at least 1 month after discontinuing high doses (2 mg/kg/day or more of prednisone equivalent) of systemic steroids given for more than 14 days.
4. Patients with HIV infection
   a. MMR should be administered unless the patient is severely immunocompromised.
   b. Varicella should be considered for asymptomatic or mildly symptomatic patients.
   c. Inactivated vaccines should be administered routinely.

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars.
To determine minimum intervals between doses, see the catch-up schedule (Table 2).

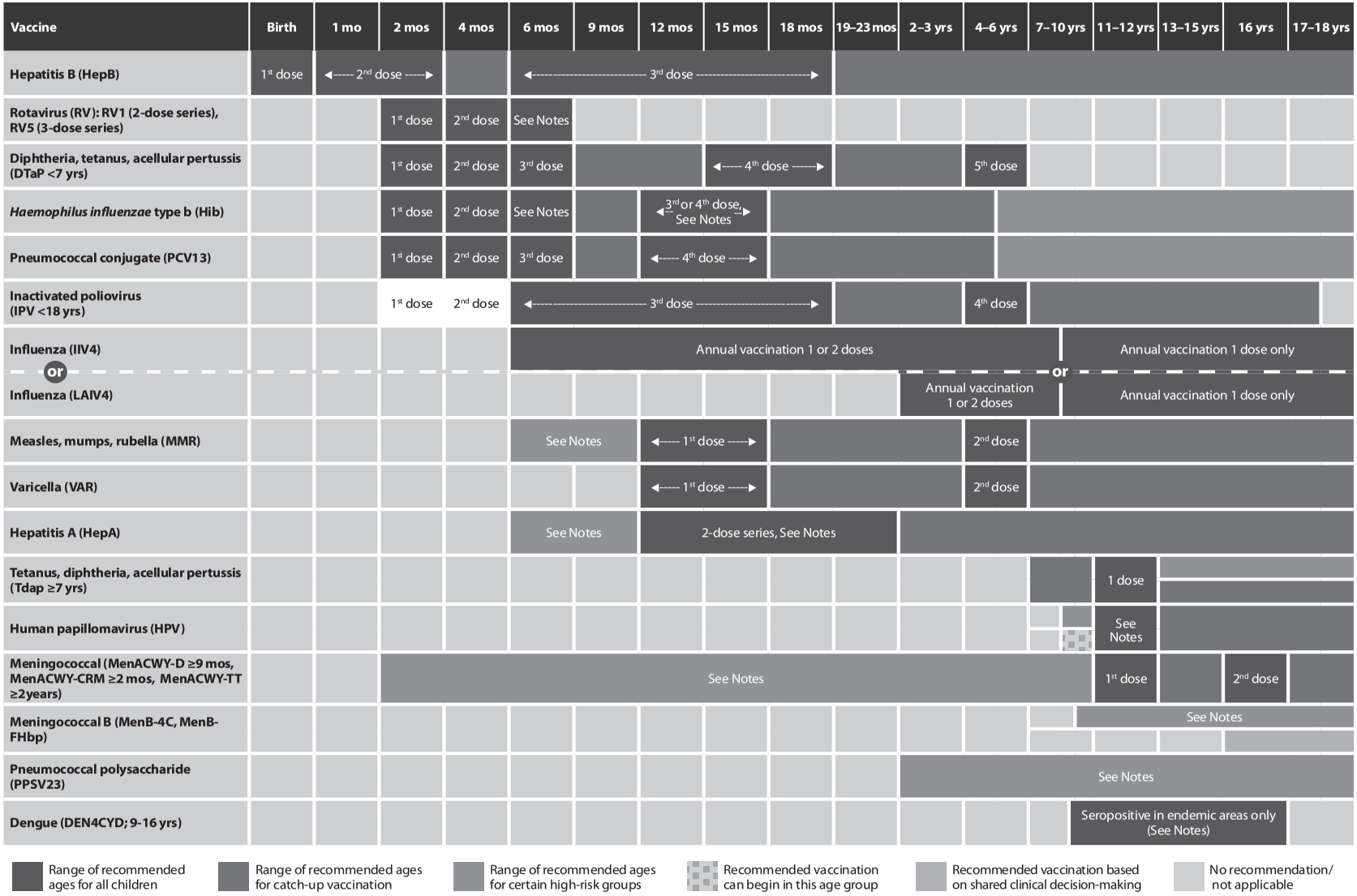


Figure 2. Recommended immunization schedule for children and adolescents 18 years or younger - United States, 2022. For those who fall behind or start late, see the catch-up schedule at https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html
Source: CDC. Use of the material, including any links to the materials on the CDC, ATSDR or HHS websites, does not imply endorsement by CDC, ATSDR, HHS or the United States Government of American College of Clinical Pharmacy or its products, facility, service, or enterprise.

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2022.

Additional information

COVID-19 Vaccination

COVID-19 vaccines are recommended for use within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html**.**

CDC's interim clinical considerations for use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html**.**

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Dengue vaccination (minimum age: 9 years)

Routine vaccination

- Age 9–16 years living in dengue endemic areas **AND** have laboratory confirmation of previous dengue infection
  - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?s_cid=rr7006a1_w and www.cdc.gov/dengue/vaccine/hcp/index.html

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix® or Quadracel®])

Routine vaccination

- 5-dose series at age 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Special situations

- Wound management in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB®, Hiberix®, Pentacel®, or Vaxelis®:** 4-dose series (3 dose primary series at age 2, 4, and 6 months, followed by a booster dose* at age 12–15 months)
  - *Vaxelis® is not recommended for use as a booster dose. A different Hib-containing vaccine should be used for the booster dose.
- **PedvaxHIB®:** 3-dose series (2-dose primary series at age 2 and 4 months, followed by a booster dose at age 12–15 months)

Catch-up vaccination

- **Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) at least 8 weeks after dose 2.
- **2 doses of PedvaxHIB® before age 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **1 dose administered at age 15 months or older:** No further doses needed
- **Unvaccinated at age 15–59 months:** Administer 1 dose.
- **Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination

For other catch-up guidance, see Table 2. Vaxelis® can be used for catch-up vaccination in children less than age 5 years. Follow the catch-up schedule even if Vaxelis® is used for one or more doses. For detailed information on use of Vaxelis® see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm.

Special situations

- **Chemotherapy or radiation treatment:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through age 14 months) OR no doses (age 15 months or older)*

Notes

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Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series (minimum interval: 6 months) at age 12–23 months

Catch-up vaccination
- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel
- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between age 12–23 months.
  - **Unvaccinated age 12 months or older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)
- **Mother is HBsAg-negative:**
  - **All** medically stable infants ≥2,000 grams: 1 dose within 24 hours of birth
  - Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series
- 3-dose series at age 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination
- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB®** only).
- Adolescents age 18 years or older may receive a 2-dose series of HepB **(Heplisav-B®)** at least 4 weeks apart.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations
- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Post-vaccination serology testing and revaccination** (if anti-HBs < 10mIU/mL) is recommended for certain populations, including:
  - **Infants born to HBsAg-positive mothers**
  - **Hemodialysis patients**
  - **Other immunocompromised persons**

For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination
- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9–14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted.
- No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.

Special situations
- **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
- **History of sexual abuse or assault:** Start at age 9 years.
- **Pregnancy:** Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV4], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination
- Use any influenza vaccine appropriate for age and health status annually:
  - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2021, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
  - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2021
  - 1 dose for **all persons age 9 years or older**
- For the 2021-2022 season, see www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm.
- For the 2022–23 season, see the 2022–23 ACIP influenza vaccine recommendations.

Special situations
- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: see Appendix listing contraindications and precautions
- **Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine:** see Appendix listing contraindications and precautions

Measles, mumps, and rubella vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series at age 12–15 months, age 4–6 years
- MMR or MMRV may be administered

Note: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination
- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.
- Minimum interval between MMRV doses: 3 months

Special situations
International travel
- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure

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Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra], 2 years [MenACWY-TT, MenQuadfi])

Routine vaccination

- 2-dose series at age 11–12 years; 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Menveo**
  - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6 and 12 months)
  - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency or complement inhibitor use:**
    - Age 9–23 months: 2-dose series at least 12 weeks apart
    - Age 24 months or older: 2-dose series at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - Age 9–23 months: Not recommended
    - Age 24 months or older: 2-dose series at least 8 weeks apart
    - **Menactra®** must be administered at least 4 weeks after completion of PCV13 series.
- **MenQuadfi®**
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/)**:**

- Children less than age 24 months:
  - **Menveo® (age 2–23 months)**
    - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6 and 12 months)
    - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
    - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - **Menactra® (age 9–23 months)**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose Menveo®, Menactra®, or MenQuadfi®

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo®, Menactra®,** or **MenQuadfi®**

Adolescent vaccination of children who received MenACWY prior to age 10 years:

- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- **Children for whom boosters are not recommended** (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

Note: Menactra® should be administered either before or at the same time as DTaP. MenACWY vaccines may be administered simultaneously with MenB vaccines if indicated, but at a different anatomic site, if feasible.

For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero®; MenB-FHbp, Trumenba®])

Shared clinical decision-making

- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero®:** 2-dose series at least 1 month apart
  - **Trumenba®:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Bexsero®:** 2-dose series at least 1 month apart
- **Trumenba®:** 3-dose series at 0, 1–2, 6 months

Note: Bexsero® and **Trumenba®** are not interchangeable; the same product should be used for all doses in a series.

For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at age 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations

Underlying conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a dose 2 of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a dose 2 of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

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Chronic liver disease, alcoholism:
Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

Poliovirus vaccination (minimum age: 6 weeks)

Routine vaccination
- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination
- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents age 18 years or older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:
- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_%20cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination
- **Rotarix®:** 2-dose series at age 2 and 4 months
- **RotaTeq®:** 3-dose series at age 2, 4, and 6 months
- If any dose in the series is either **RotaTeq®** or unknown, default to 3-dose series.

Catch-up vaccination
- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination
- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36.
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination
- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- **Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at age 7–10 years:**
  - **Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
  - **Children age 10 years** who receive Tdap do not need the routine Tdap dose at age 11–12 years.
- **DTaP inadvertently administered on or after age 7 years**:
  - **Children age 7–9 years**: DTaP may count as part of catch-up series. Administer routine Tdap dose at age 11–12 years.
  - **Children age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.

Special situations
- **Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.
- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older

Varicella vaccination (minimum age: 12 months)

Routine vaccination
- 2-dose series at age 12–15 months, 4–6 years
- VAR or MMRV may be administered*
- Dose 2 may be administered as early as 3 months after dose 1 (a dose inadvertently administered after at least 4weeks may be counted as valid)

***Note**: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination
- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have a 2-dose series:
  - **Age 7–12 years**: routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
  - **Age 13 years and older**: routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of MMRV is 12 years.

V. PEDIATRIC SEIZURE DISORDERS

A. Incidence of Pediatric Seizures
   1. Over 470,000 children in the United States with active epilepsy
   2 Highest incidence in infants and decreases to less than 1% of children aged 6-17 years old.
   3. Higher incidence with lower socioeconomic status and pre-existing developmental delays/disabilities
   4. Additional risk factors for seizures include trauma, infection, fever, metabolic imbalances, toxic ingestions, drug withdrawal, neurologic conditions, and medications

B. Febrile Seizures
   1. Febrile seizures are the most common seizure disorder in childhood
   2. Affects 2%–5% of children between the ages of 6 and 60 months
   3. Simple versus complex febrile seizures
      a. Simple: brief (less than 15 minutes) generalized seizures that occur once during a 24-hour period in a febrile child; no evidence of intracranial infection, metabolic disturbance, or history of febrile seizures
      b. Complex: one of the following in a febrile child
         i. Prolonged (more than 15 minutes) seizure
         ii. Focal seizure
         iii. Occur more than once in a 24-hour period
   4. Risk of developing epilepsy
      a. Children with simple febrile seizures have approximately the same risk of developing epilepsy as general population (about 1%)
      b. Higher risk if febrile seizures are recurrent, age younger than 12 months at time of first febrile seizure, or have a family history of epilepsy
   5. High rate of recurrence even for simple febrile seizure
      a. First simple febrile seizure at less than 12 months old: 50% probability of recurrence
      b. First simple febrile seizure at 12 months or older: 30% probability of recurrence
      c. Second simple febrile seizure: 50% probability of at least one recurrence
   6. Management of simple febrile seizures:
      a. Generally benign with excellent prognosis
      b. Risk of recurrence can be reduced with the following therapies; however, potential toxicities outweigh benefits, and these are not routinely recommended:
         i. Phenobarbital long-term therapy
         ii. Primidone long-term therapy
         iii. Valproic acid long-term therapy
         iv. Oral diazepam intermittent therapy for fevers
      c. Oral diazepam at fever recurrence can be considered when parental anxiety is severe
      d. Antipyretics are ineffective in preventing febrile seizures

C. Metabolic causes of pediatric afebrile seizures
   1. A metabolic screen should be considered with afebrile seizures, including glucose electrolytes with calcium and magnesium, and renal function.
   2. More extensive metabolic testing looking for inborn errors of metabolism should be considered if other suggestive symptoms are present, including unexplained global delay or regression, organomegaly, unusual odor, similarly affected siblings, or an acute presentation with altered level of consciousness, multiorgan dysfunction, and vomiting.
   3. Several metabolic causes of seizures can be treated. Examples include:
      a. Pyridoxine-dependent or pyridoxal-5-phosphate-dependent epilepsy (NOTE: pyridoxine is frequently empirically trialed in refractory seizures in infants younger than 1 year)

b. Biotinidase deficiency
c. Glucose transporter deficiency
d. Cerebral folate deficiency
e. Creatine deficiency
f. Serine deficiency

D. Treatment Options Based on Seizure Type (Table 6)

Table 6. Treatment Options Based on Seizure Type

Seizure Type	Drugs of Choice	Alternatives
Neonatal	PB	LEV, PHT
Focal (formerly "partial")	CBZ, PHT, LTG, LEV, oxcarbazepine, topiramate, ZNS	PB, gabapentin, tiagabine, lacosamide, VPA[a]
Generalized		
Tonic-clonic	CBZ, PHT, LTG, LEV, ZNS	Topiramate, VPA[a]
Myoclonic	VPA[a], LEV	LTG, topiramate, ZNS, clobazam, rufinamide, felbamate
Absence	Ethosuximide, VPA[a]	Lamotrigine, methsuximide, ZNS
Lennox-Gastaut	VPA[a], topiramate, lamotrigine	Rufinamide, CBD, clobazam, felbamate, ZNS
Infantile spasms	ACTH injectable gel	Vigabatrin, lamotrigine, tiagabine, topiramate, VPA[a], ZNS

[a]Valproic acid can cause major congenital malformations and has a U.S. black box warning stating that it should not be administered to women of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.

ACTH = adrenocorticotropic hormone; CBD = cannabidiol; CBZ = carbamazepine; LEV = levetiracetam, LTG = lamotrigine; PB = phenobarbital; PHT = phenytoin; VPA = valproic acid; ZNS = zonisamide.

E. Comparison of Available Antiseizure Drugs (Table 7)

Table 7. Comparison of Available Antiseizure Drugs

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Brivaracetam	Dizziness Sleepiness Nausea and vomiting Behavioral reactions	Substrate of CYP2C19	Poor metabolizers of CYP2C19 may require dose reduction FDA-approved medication guide must be dispensed with medication
Cannabidiol	Somnolence/fatigue Increased liver enzymes Hypersensitivity reactions Decreased appetite and weight loss Diarrhea Insomnia	Moderate inhibitor of CYP2C19 High-fat/high-calorie meals increase extent of absorption	Schedule C-V Sugar-free oral solution
Carbamazepine	Rash (Black Box Warning) Hyponatremia ↓ Bone density Teratogenic DRESS syndrome Bone marrow suppression	Autoinduction ↓ Effectiveness of OCs Major CYP3A4 substrate	Significant drug interactions Routine therapeutic drug monitoring NIOSH hazardous drug HLA-B*1502 associated with SJS/TEN

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Clobazam	Somnolence	Dose adjustment needed in hepatic impairment Dose adjustment needed in CYP2C19 poor metabolizers Long half-life	Long-acting benzodiazpine Tolerance may develop over time
Eslicarbazepine	Dizziness Nausea Diplopia	Substrate of UGT2B4 Moderate inducer of CYP3A4 Dose adjustment needed with renal impairment. Avoid use in severe hepatic impairment.	Significant drug interactions NIOSH hazardous drug
Ethosuximide	Abdominal pain, anorexia, diarrhea Drowsiness	Substrate of CYP3A4	Ineffective for seizure types other than absence
Felbamate	Anorexia, nausea, weight loss Insomnia, somnolence Aplastic anemia Hepatic failure	Clearance approximately 50:50 renal/hepatic	Significant drug interactions Aplastic anemia: Adults > children Requires signed informed consent
Fenfluramine	CNS depression ↓ Appetite, weight loss Hypertension Ocular effects (glaucoma) Pulmonary hypertension (Black Box Warning) Serotonin syndrome Valvular heart disease (Black Box Warning)	Major substrate of CYP1A2 and CYP2B6 Minor substrate of CYP2C19, CYP2C9, CYP2D6, and CYP3A4 Avoid use with hepatic impairment Avoid use with moderate to severe renal impairment	REMS program due to pulmonary hypertension and valvular heart disease risk Potential drug interaction with clobazam and stiripentol warranting dose reduction of fenfluramine
Gabapentin	Somnolence Weight gain	↑ Clearance in children < 6 yr Dose adjustment needed in renal insufficiency (no specific recommendations/studies for < 12 years old) Nonlinear pharmacokinetics	Minimal drug interactions Minimal cognitive effects May worsen Lennox-Gastaut
Lacosamide	Prolonged PR interval Dizziness Headache Diplopia	Dose adjustment needed in severe renal insufficiency	Use with caution if severe cardiac disease or conduction problems; caution with beta-blockers and some Ca channel blockers because of potential prolonged PR interval, AV block, or bradycardia No other clinically significant drug interactions
Lamotrigine	Rash/SJS/DRESS syndrome (Black Box Warning)	Autoinduction	Rash: Children > adults Minimal cognitive effects NIOSH hazardous drug
Levetiracetam	Headache Somnolence Behavioral changes	Renal excretion Clearance 40% ↑ in children No effect on CYP system	Minimal drug interactions Behavioral effects (e.g., aggression, agitation, mood changes): children > adults
Oxcarbazepine	Hyponatremia (> CBZ) Rash (< CBZ but has cross-reactivity with CBZ)	Clearance 40% ↑ in children < 6 yr Induces CYP3A4 Inhibits CYP2C19 ↓ Effectiveness of OCs	Hyponatremia: adults > children Minimal cognitive effects NIOSH hazadous drug

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Perampanel	Dizziness Nausea Somnolence Fatigue Irritability Headache	Substrate of CYP3A4 Minor substrate of CYP1A2 and CYP2B6	Black box warning for neuropsychiatric events
Phenobarbital	Cognitive dysfunction Sedation Rash ↓ Bone density DRESS syndrome	High Protein Binding ↓ Effectiveness of OCs Autoinduction Long half-life	Significant drug interactions Routine therapeutic drug monitoring
Phenytoin and Fosphenytoin	Rash Gingival hyperplasia Hirsutism ↓ Bone density Teratogenic Phlebitis and extravasation DRESS syndrome Arrhythmias	Nonlinear pharmacokinetics ↓ Effectiveness of OCs	Significant drug interactions NIOSH hazardous drug Reduced risk of extravasation and hypotension with fosphenytoin Routine therapeutic drug monitoring HLA B*1502 associated w/increased risk of SJS/TEN Shake well before use Adheres to feeding tubes
Pregabalin	Somnolence Behavioral problems Dizziness Weight gain Ataxia Angioedema	AUC is ~30% lower while fasting	Minimal drug interactions
Rufinamide	Somnolence Rash QT interval shortening	↑ Level with concurrent VPA	Somnolence: Minimized with slow dose titration Rash: All reported cases are in children Administer with food
Stiripentol	Appetite/weight loss Drowsiness/dizziness Neutropenia Thrombocytopenia	↓ Clearance with increasing body weight (adolescents may require lower dosing than younger children) Valproate dose reduction by 30% may help minimize appetite/weight loss Systemic exposure is slightly higher with the powder for suspension than with capsules	Not approved for use as monotherapy. Should be used with clobazam (labeled use) or valproate (off-label) Approved for use in Dravet syndrome
Tiagabine	Dizziness Nonconvulsive status epilepticus (case reports)	Clearance 50% ↑ in children	Minimal cognitive effects
Topiramate	Cognitive dysfunction Weight loss Glaucoma Oligohidrosis Metabolic acidosis Nephrolithiasis	↑ Clearance in children Dose adjustment needed in renal insufficiency	Weight loss more common in obese patients Children at higher risk of oligohidrosis than adults NIOSH hazardous drug

Table 7. Comparison of Available Antiseizure Drugs *(Cont'd)*

Drug	Adverse Effects	Pharmacokinetic Considerations	Other Comments
Valproic acid	Weight gain Menstrual irregularities Polycystic ovarian syndrome Hyperandrogenism Hepatotoxicity (Black Box Warning) Teratogenic (Black Box Warning) Thrombocytopenia Pancreatitis (Black Box Warning)	CYP induction > in children	Significant drug interactions; Most cases of hepatotoxicity in children < 2 yr old (often if multiple AEDs) NIOSH hazardous drug Routine therapeutic drug monitoring Use sprinkles (opened caps) on food for ease of administration in small children
Vigabatrin	Vision loss (Black Box Warning) Weight gain		Available only through restricted distribution program NIOSH hazardous drug
Zonisamide	Weight loss Rash Oligohidrosis Somnolence Agitation Hallucinations Metabolic acidosis Nephrolithiasis	Primarily renal excretion No effect on CYP system	Better tolerated by children than by adults NIOSH hazardous drug

CBZ = carbamazepine; CYP = cytochrome P450; DRESS = drug reaction with eosinophilia and systemic symptoms; NIOSH = National Institute for Occupational Safety and Health; OC = oral contraceptive; PHT = phenytoin; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; VPA = valproic acid; ↓ = decreased; ↑ = increased.

Patient Case

10. A 14-year-old female adolescent with moderate obesity comes to the clinic with an erythematous pruritic rash. She was given oxcarbazepine about 3 weeks ago for the management of focal seizures. Her medical history is significant only for seizures. She recently became sexually active with a male and admits inconsistent contraceptive use. Which intervention is best for her?

    A. Change to carbamazepine.

    B. Change to levetiracetam.

    C. Change to valproic acid.

    D. No change in therapy is necessary.

VI. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. Clinical Presentation
   1. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* criteria
      a. Either (i) or (ii) or combined presentation when all core features present
         i. Six or more (five or more if 17 years or older) of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate:
            (a) Often does not give close attention to detail; makes careless mistakes
            (b) Often has trouble keeping attention on tasks and activities
            (c) Often does not seem to listen
            (d) Often does not follow instructions

(e) Often has trouble organizing activities
(f) Often avoids or dislikes things that require long periods of mental effort
(g) Often loses things needed for tasks or activities
(h) Often is easily distracted
(i) Often is forgetful

ii. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to a point that is disruptive and inappropriate:
(a) Hyperactivity
(1) Often fidgets or squirms
(2) Often is unable to remain seated when it is expected
(3) Often runs or climbs when and where it is not appropriate
(4) Often has difficulty with quiet play or activities
(5) Often is "on the go"
(6) Often talks excessively
(b) Impulsivity
(1) Often blurts out answers
(2) Often has difficulty waiting one's turn
(3) Often interrupts

b. Some symptoms were present by 12 years of age.
c. Some impairment from the symptoms is present in two or more settings.
d. Clear evidence of significant impairment exists in social, school, or work functioning.
e. No other mental disorder better describes the symptoms.

2. Comorbid disease states: 44%–87% of children with ADHD have at least one other disorder
a. Oppositional defiant disorder
i. Most common comorbid disorder in adolescents
ii. Presence of ADHD increases the odds of oppositional defiant disorder almost 11-fold.
b. Anxiety disorder: May exist in about 25% of children with ADHD
c. Tics
i. 21%–90% of children with Tourette syndrome may also have ADHD.
ii. May not be exacerbated by stimulant agents, as once thought

Patient Case

11. A 9-year-old boy has a new diagnosis of ADHD. At school, he is disruptive, talks when the teacher is talking, and runs around the classroom. His parents report extreme difficulty in getting him to do his homework after school. Which is best for his initial drug therapy?

A. Methylphenidate OROS (Concerta) given once daily.
B. Methylphenidate immediate release (Ritalin) given twice daily, with doses administered 4 hours apart.
C. Guanfacine given at bedtime.
D. D-Methylphenidate (Focalin) given twice daily, with doses administered 4 hours apart.

B. Classification: Based on *DSM-5* Criteria
1. ADHD, combined type: Criteria (i) and (ii) both are met.
2. ADHD, predominantly inattentive type: Criterion (i) is met, but (ii) is not met.
3. ADHD, predominantly hyperactive-impulsive type: Criterion (ii) is met, but (i) is not met.

C. Treatment Options: Combination of pharmacotherapy and behavioral therapy is more beneficial than either intervention alone.
   1. Factors affecting choice of pharmacologic agent
      a. Desired length of coverage time for symptoms
         i. Consider time of day when symptoms occur.
         ii. Consider time of day when child's activities occur (e.g., when is homework done, at what time are teenagers driving, when is child's bedtime).
      b. Child's ability to swallow pills or capsules
      c. Concomitant disease states (e.g., tic disorders)
      d. Adverse effect profile
      e. Concerns about abuse or diversion potential
         i. Children with ADHD are more likely to have a concurrent substance use disorder than those without ADHD.
         ii. Treatment with stimulant medication can reduce the risk of developing a substance use disorder.
         iii. Children treated with stimulants at a younger age are less likely to misuse or abuse substances than those in whom treatment is delayed.
      f. Expense
   2. Available pharmacologic agents
      a. Stimulant medications: Highly effective for most children in reducing core symptoms of ADHD. Some children with ADHD respond better to one stimulant type than another; therefore, both methylphenidate- and amphetamine-containing products should be tried before stimulant treatment is deemed a failure. Stimulant medications vary in duration of action (see Table 8). Ideally, the duration of action of the medication selected should match the duration needed for symptom control.
         i. Methylphenidate-containing products
            (a) Ramp effect: Behavioral effects are proportional to the rate of methylphenidate absorption into the central nervous system.
            (b) See Table 8 for a comparison of available products.
            (c) Adverse effects and precautions
               (1) Headache, stomachache, loss of appetite, and insomnia
               (2) Use with caution in patients with glaucoma, tics, psychosis, and concomitant monoamine oxidase inhibitor use.
               (3) Insomnia, anorexia, and tics occur more often with transdermal patch; also mild skin reactions.
         ii. Amphetamine-containing products
            (a) See Table 8 for a comparison of available products.
            (b) Adverse effects and precautions
               (1) Loss of appetite, insomnia, abdominal pain, and nervousness
               (2) Can exacerbate preexisting hypertension and tic disorders
               (3) Labeling change warns of potential association with sudden cardiac death (SCD); therefore, these are not recommended for patients with known structural heart defects.
         iii. Potential association with SCD
            (a) No established evidence of causative relationship between stimulants and SCD
            (b) The frequency of SCD is no higher in children taking stimulants than in the general pediatric population.
            (c) The AAP recommends targeted cardiac history and careful physical examination before initiating stimulant therapy.
               (1) Routine electrocardiography is not recommended unless history and physical examination suggest cardiac disease.

(2) For otherwise healthy children, stimulant therapy should not be withheld because of the inability to obtain an electrocardiogram or assessment by a pediatric cardiologist.

b. Non-stimulant medications: Demonstrated efficacy in reducing core symptoms of ADHD; however, less evidence to date compared with stimulant medications.
   i. Norepinephrine reuptake inhibitors (see Table 9): FDA-approved for the treatment of ADHD
      (a) Adverse effects: Dyspepsia, decreased appetite, weight loss, and fatigue
      (b) Labeling change warns of potential for severe liver injury, although routine monitoring of hepatic function is not necessary.
      (c) Black box warning about increased risk of suicidal ideation in children and adolescents
      (d) Does not exacerbate tics
   ii. α-Adrenergic receptor agonists (see Table 9): FDA-approved for the treatment of ADHD
   iii. Antidepressants: Non-FDA label approved for the treatment of ADHD
      (a) Noradrenergic antidepressant (e.g., bupropion [Wellbutrin])
         (1) Can use immediate- or extended-release product given in two or three doses
         (2) Contraindicated for children with active seizure disorder
      (b) Tricyclic antidepressants (e.g., imipramine, nortriptyline)
         (1) Baseline electrocardiogram is recommended before therapy initiation and after each dose increase.
         (2) Desipramine should be used with extreme caution because of reports of sudden death.

3. AAP recommendations for treatment
   a. Children 4-5 years old:
      i. Behavior therapy as first-line treatment
      ii. Methylphenidate as second-line treatment
   b. Children 6-11 years old:
      i. Medication and behavioral therapy as first-line treatment
         (a) Stimulants have better evidence
         (b) Non-stimulants may be considered but evidence is weaker
   c. Adolescents 12-18 years old:
      i. Medication (with assent of child) as first-line treatment
         (a) Any FDA-approved medication
      ii. May also consider behavioral treatment

Table 8. Stimulant Agents for the Treatment of ADHD

Medication	Doses per Day	Onset of Effect	Duration of Effect (hr)	Other Comments
Methylphenidate-Containing Products				
Methylphenidate immediate release (Ritalin, Methylin chewable tablets, Methylin oral solution)	2 or 3	20–60 min	3–5	50:50 racemic mixture of l-threo and d-threo isomers
Dexmethylphenidate (Focalin)	2 or 3	20–60 min	3–5	Only D-threo isomer, thought to be pharmacologically active enantiomer D-Threo isomer has not been shown to hinder effectiveness or increase adverse effects Recommended doses are half those of methylphenidate immediate release Offers no proven pharmacoeconomic benefit over methylphenidate immediate-release products

ADHD = attention-deficit/hyperactivity disorder.

Table 8. Stimulant Agents for the Treatment of ADHD *(Cont'd)*

Medication	Doses per Day	Onset of Effect	Duration of Effect (hr)	Other Comments
Methylphenidate-Containing Products (*cont'd*)				
Methylphenidate sustained release (Ritalin SR)	1 or 2	1–3 hr	2–6	
Methylphenidate extended release (Ritalin LA)	1	20–60 min	6–8	Contains 50% immediate-release and 50% extended release beads Capsule may be opened and sprinkled on applesauce Efficacy may wane in after-school or late-afternoon hours, necessitating addition of methylphenidate immediate release for later-day coverage
Methylphenidate modified release (Metadate CD)	1	20–60 min	6–8	Capsule contains 30% immediate-release and 70% extended-release beads (slowly released about 4 hr after ingestion) Capsule may be opened and sprinkled on applesauce Efficacy may wane in after-school or late afternoon hours, necessitating addition of methylphenidate immediate release for later-day coverage
Methylphenidate extended release chewable tablet (QuilliChew ER)	1	45 min	8	Alcohol concentration of 40% resulted in 90% of the methylphenidate being released in the first hour; avoid consuming alcohol during therapy.
Dexmethylphenidate extended release (Focalin XR)	1	20–60 min	8–12	Bimodal drug release results in peak serum concentrations at 1½ and 6½ hr after dose administration Shorter duration of action than methylphenidate OROS, so afternoon symptom control is not as good
Serdexmethylphenidate and dexmethylphenidate (Azstarsys)	1 (peak 2)	60 min	10	Each capsule contains a fixed molar ratio of 30% dexmethylphenidate and 70% serdexmethylphenidate Serdexmethylphenidate is a pro-drug of dexmethylphenidate, which is converted in the lower gastrointestinal tract
Methylphenidate extended release (Metadate ER, Relexxii)	1	60 min	12	
Methylphenidate OROS (Concerta)	1	20–60 min	12	Outer capsule contains about 22% of the drug, allowing immediate release; tablet core contains remainder of drug, which is released over 10 hr, minimizing peak to trough fluctuations Swallow whole; *do not* chew, crush, or divide
Methylphenidate orally disintegrating tablet (Cotempla XR-ODT)	1	60 min	12	Contains 25% IR and 75% ER methylphenidate. Tablet should remain in blister pack until ready to use. Do not crush or chew. Place on tongue to disintegrate.
Methylphenidate transdermal system (Daytrana)	1	60 min	11–12	Apply to hip 2 hr before effect is needed Recommended to remove 9 hr after application; can be worn up to 16 hr Duration of effect is about 3 hr after patch removal Can be worn while swimming or exercising

ADHD = attention-deficit/hyperactivity disorder.

Table 8. Stimulant Agents for the Treatment of ADHD *(Cont'd)*

Medication	Doses per Day	Onset of Effect	Duration of Effect (hr)	Other Comments
Methylphenidate-Containing Products (*cont'd*)				
Methylphenidate reconstituted oral suspension (Quillivant XR)	1	45 min	12	Contains sodium benzoate. Banana flavor. Store reconstituted suspension in original container for up to 4 months. Shake bottle ≥10 seconds prior to administration. Use the oral dosing dispenser provided. Once reconstituted with water forms an extended release suspension that contains approximately 20% immediate release and 80% extended release methylphenidate.
Methylphenidate extended release (Aptensio XR, Adhansia XR, Jornay PM)	1	2 hr	12	Contains multi layered beads.
Amphetamine-Containing Products				
Mixed amphetamine salts immediate release (Adderall)	1-3	20–60 min	6	
Amphetamine/ dextroamphetamine tablets (Evekeo)	1-3	45 min	6	Contains d-amphetamine and l-amphetamine in a 1:1 ratio.
Dextroamphetamine oral solution (ProCentra)	1-3	60 min	4-6	Bubblegum flavor. Shake suspension well before administration.
Dextroamphetamine immediate-release tablets (Zenzedi)	1–2	30–90 min	4–6	
Dextroamphetamine extended release capsule (Dexedrine spansules)	1-2	60-90 min	6-8	Bead-filled capsule (50% released immediately, 50% delayed release)
Mixed amphetamine salts extended release (Adderall XR)	1	20–60 min	10-12	Contains 50% immediate-release and 50% extended release beads (released 4 hr after ingestion) Can be sprinkled on applesauce
Amphetamine extended release oral suspension (Dyanavel XR, Adzenys ER)	1	60 min	12	Contains d-amphetamine and l-amphetamine in a 3:1 ratio. Shake bottle before use
Amphetamine extended release oral disintegrating tablets (Adzenys XR-ODT)	1	20-60 min	10-12	Store in travel case provided.
Lisdexamfetamine dimesylate (Vyvanse)	1	60 min	10–12	Prodrug with D-amphetamine covalently bound to L-lysine Designed for less abuse potential than amphetamine No clinical evidence of superiority over other amphetamine products
Mixed amphetamine salts extended release (Mydayis)	1	2-4 hr	16	Administer immediately after waking due to long duration. May open capsule and sprinkle contents on food.

ADHD = attention-deficit/hyperactivity disorder.

Table 9. Non-stimulant Agents for the Treatment of ADHD

Medication	Doses per Day	Onset of Effect (wk)	Duration of Effect (hr)	Other Comments
Norepinephrine Reuptake Inhibitor				
Atomoxetine	1 or 2	2–4	10–12	Can be considered first-line therapy for children with active substance abuse problem, comorbid anxiety, or tics Metabolized through CYP2D6
Viloxazine extended release	1	1	24	May increase heart rate and blood pressure May induce manic episodes in patients with bipolar disorder May cause somnolence and fatigue
α-Adrenergic Receptor Agonists				
Clonidine extended release	1 or 2	1–2	10–12	May be more effective for hyperactivity than for inattention symptoms Lessens severity of tics, especially when used in combination with methylphenidate Primary adverse effect is sedation
Guanfacine extended release	1	1–2	10–12	Improves comorbid tic disorder Less sedating than clonidine Abrupt discontinuation can cause rebound hypertension

ADHD = attention-deficit/hyperactivity disorder.

Patient Case

12. The patient in question 11 has been doing well in school since methylphenidate (OROS) (Concerta) was initiated 6 months ago. His late-afternoon symptoms are well controlled; however, he has had insomnia since drug therapy initiation. Which is the best modification to his treatment regimen?

    A. Administer the Concerta dose later in the day.

    B. Change to methylphenidate modified release (Metadate CD) once a day.

    C. Change to methylphenidate transdermal patch (Daytrana).

    D. Change to atomoxetine at bedtime.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Group B *Streptococcus*, *Escherichia coli*, *Klebsiella* spp., and *Listeria* spp. are the most likely pathogens of neonatal sepsis or meningitis. Ampicillin plus ceftazidime administered at meningitic doses would provide reasonable empiric coverage (Answer B is correct). Ampicillin plus gentamicin is a reasonable alternative regimen. Cefotaxime or ceftazidime (when cefotaxime is unavailable) may be preferred to gentamicin because of its better penetration into the cerebrospinal fluid in meningitis caused by gram-negative organisms. In general, ceftazidime (or cefotaxime when available) use should be reserved for such cases because overuse of this agent has been associated with increased resistance and increased risk of invasive candidiasis. Although coagulase-negative *Staphylococcus* is the most likely cause of nosocomial neonatal sepsis, this patient's early presentation makes a hospital-acquired pathogen extremely unlikely. Therefore, vancomycin is unnecessary (Answer A is incorrect). Ampicillin plus ceftriaxone would provide adequate empiric antimicrobial coverage for the most likely pathogens. However, ceftriaxone use can result in biliary sludging, leading to reduced elimination of bilirubin and a potential risk of kernicterus in neonates (Answer C is incorrect). Ceftazidime plus gentamicin lacks coverage for *Listeria* and group B *Streptococcus,* which is still necessary empirically even though the mother received penicillin before delivery. In addition, empiric double-coverage of gram-negative organisms is not necessary for early onset neonatal sepsis (Answer D is incorrect).

2. Answer: C

Given this patient's age and culture results, the most likely infecting organism is *E. coli* or *Klebsiella* spp. (gram-negative rods), for which antimicrobial prophylaxis is not indicated (Answer C is correct). The most common pathogens causing meningitis in neonates do not warrant antimicrobial prophylaxis. If this patient were older and infected with *N. meningitidis* or *H. influenzae,* antibiotic prophylaxis with rifampin would be indicated for all close contacts, regardless of age or immunization status (Answers A and D are incorrect). Rifampin prophylaxis to eliminate nasal carriage is also indicated for people who receive index diagnoses of *N. meningitidis* and treatment with an antibiotic other than ceftriaxone (Answer B is incorrect).

3. Answer: C

The most likely causative organisms of sepsis or meningitis in this age group are *S. pneumoniae* and *N. meningitidis*. Therefore, a regimen of ceftriaxone plus vancomycin would provide appropriate empiric coverage (Answer C is correct). Depending on the regional incidence of resistant *S. pneumoniae,* empiric vancomycin might not be necessary. Ampicillin plus gentamicin would not provide adequate coverage (Answer A is incorrect). Cefuroxime does not provide reliable penetration into the cerebrospinal fluid; therefore, it would not be appropriate empiric coverage because this patient's presentation suggests that he has meningitis (Answer B is incorrect). Rifampin would be the drug of choice for the prophylaxis of close contacts if this patient receives a diagnosis of meningococcal meningitis; however, it is inadequate for treatment (Answer D is incorrect).

4. Answer: B

Palivizumab is the drug of choice for prophylaxis against RSV infection in high-risk patient populations, including those born before 29 weeks' gestation, regardless of risk factors, who are 12 months or younger during RSV season (Answer B is correct). Patients born between 29 and 32 weeks' gestation are not considered high risk because of their gestational age (Answer C is incorrect). To be considered as candidates for palivizumab prophylaxis, these infants must have a disease state (e.g., chronic lung disease, hemodynamically significant heart disease, airway anomalies, neuromuscular disease, profound immunodeficiency) that places them at risk of severe RSV infection. Other potential risk factors (e.g., siblings younger than 5 years or day care attenders) are no longer considered when determining the appropriateness of palivizumab prophylaxis. Patients with complex heart defects needing surgical repair are at high risk of developing severe RSV infections; however, after the repair is complete, palivizumab is no longer warranted (Answer D is incorrect). Patients with a history of chronic lung disease who are 24 months or younger and who are receiving, or have received in the past 6 months, oxygen or medical management for chronic lung disease are also at risk of severe RSV infection (Answer A is incorrect).

5. Answer: D

There is no specific treatment for RSV infection. Intravenous fluids, oxygen, and mechanical ventilation, if needed, are indicated (Answer D is correct). Palivizumab is the drug of choice for RSV prophylaxis, but it has no role in treatment (Answer A is incorrect). Corticosteroids have not been shown to be of benefit and are therefore not indicated (Answer B is incorrect). Secondary bacterial infection with *H. influenzae* or *M. catarrhalis* can occur; however, empiric antibiotic therapy is not indicated (Answer C is incorrect).

6. Answer: A

Persistence of middle ear fluid after an episode of AOM is common. If these findings are not associated with signs and symptoms of infection, a diagnosis of OME is made. The AAP practice guideline for the management of OME recommends watchful waiting (Answer A is correct). A watch-and-wait approach would not be appropriate for this patient if she were given a diagnosis of AOM rather than OME, because she is younger than 6 months. Spontaneous resolution of OME occurs within 3 months in 75%–90% of cases after AOM without residual morbidities. Children at high risk of speech and learning problems (e.g., craniofacial anomalies, Down syndrome, severe visual impairment) may need earlier, more aggressive intervention (e.g., tympanostomy tubes). Decongestants and antihistamines do not promote resolution or improve symptoms (Answer C is incorrect). Antibiotics are not effective in treating OME (Answer B is incorrect). However, high-dose amoxicillin (80–100 mg/kg/day) is considered first-line therapy for AOM. If this patient's treatment with the initial course of lower-dose amoxicillin fails (which is not a recommended regimen) or if she develops new signs of infection, then high-dose amoxicillin will be an appropriate treatment choice. Up to 74% of streptococcal strains have been reported to be resistant to azithromycin, which also has poor activity against *H. influenzae*; therefore, this would not be the best antibiotic option if an infection developed (Answer D is incorrect).

7. Answer: C

Four cases of otitis media in 12 months is considered recurrent otitis media, for which the watch-and-wait approach is not recommended (Answer D is incorrect). Previously, this patient would have been a candidate for antibiotic prophylaxis; however, this practice has fallen out of favor because of the significant risk of antimicrobial resistance compared with the minor reduction in the occurrence of otitis media (Answer A is incorrect). Tympanostomy tubes are typically reserved for patients in whom aggressive antibiotic therapy fails, and they may be effective only in otitis with bulging tympanic membrane (Answer B is incorrect). In addition, the greatest benefit of tympanostomy tubes is in patients with persistent OMEs resulting in significant hearing loss. As long as this patient continues to respond to high-dose amoxicillin, this will be considered a first-line regimen (Answer C is correct). In addition, the pneumococcal and influenza vaccines should be administered according to the recommended schedule, because these organisms are common causes of AOM.

8. Answer: D

Vaccines are often deferred for inappropriate reasons, leading to missed opportunities for immunization. Previous administration of IVIG can decrease the efficacy of live vaccines, such as MMR and varicella, but it does not affect the efficacy of inactivated products (Answer D is correct). The suggested interval between an IVIG dose and the administration of live vaccines depends on the immune globulin product and indication. Concerns about an association between MMR vaccine and the development of autism and immunizations overwhelming the immune system have been disproved by scientific evaluation (Answers A and C are incorrect). The MMR vaccine is grown in chick embryo tissue; however, an egg allergy is not a contraindication to its administration (Answer B is incorrect).

9. Answer: A

Immunocompromised patients should not receive live vaccines; therefore, the MMR and varicella vaccines should be deferred in these patients (Answer A is correct). Mild coldlike symptoms, or administration of antibiotics for mild illnesses, such as otitis media, are not a contraindication to vaccination, and deferring immunizations for such reasons is considered a missed opportunity (Answer B is incorrect). Patients with HIV, especially those with asymptomatic disease, should be considered candidates for all age-appropriate vaccines, including those containing live virus and the pneumococcal vaccine (Answer C is incorrect). Corticosteroid administration is an indication for deferral of live vaccines only if the patient is receiving high doses (more than 2 mg/kg/day of prednisone equivalent) for more than 14 days (Answer D is incorrect).

10. Answer: B

Rash associated with antiepileptic drugs is a common adverse effect, and it generally resolves within a few days after discontinuation. There is no reliable method to determine whether the rash will remain benign or progress to a more severe skin reaction; therefore, discontinuation of the offending drug is warranted (Answer D is incorrect). Carbamazepine has a higher incidence of rash than oxcarbazepine does, and cross-reactivity has been noted (Answer A is incorrect). Valproic acid is a good choice for managing focal seizures, and it has a low incidence of rash. However, the principal adverse effects of valproic acid include weight gain and menstrual irregularities, both of which would be undesirable in this overweight teenager. In addition, valproic acid is a known teratogen (pregnancy category D) that should be avoided if other options are available in girls of reproductive age who are unreliable in their use of contraception (Answer C is incorrect). Levetiracetam (pregnancy category C) has a low incidence of rash and minimal drug interactions (Answer B is correct).

11. Answer: A

Stimulants, especially methylphenidate, are generally considered first-line therapy for treating ADHD. Because this patient shows symptoms at school and at home, the short duration of action (3–5 hours) of a twice-daily methylphenidate immediate-release regimen will probably not provide adequate symptom relief (Answer B is incorrect). Likewise, D-methylphenidate has a short duration of action. In addition, D-methylphenidate is no more effective and has no fewer adverse effects than methylphenidate immediate release. Therefore, D-methylphenidate is generally not considered cost-effective (Answer D is incorrect). Extended-release guanfacine is approved by the FDA for the treatment of ADHD, but the evidence for children age 6–12 years is strongest with stimulants, followed by atomoxetine, and then extended-release guanfacine. Although this agent would not be the best first-line option, it may be considered, especially in children who also have a tic disorder. (Answer C is incorrect). Methylphenidate (OROS) with its longer duration of action (10–12 hours) would provide the best coverage (Answer A is correct). Therapy with this drug can be initiated without previous titration using methylphenidate immediate release.

12. Answer: C

Changing to a methylphenidate transdermal patch allows flexibility in the duration of drug effect. Wearing the patch for 9 hours results in about 12 hours of therapeutic effect; however, the patch can be removed sooner, thus reducing the duration of effect and allowing serum concentrations to decrease before bedtime (Answer C is correct). Response rates to atomoxetine are lower than to methylphenidate (OROS) in children with ADHD. In addition, the onset of therapeutic effect for atomoxetine is delayed (typically 2–4 weeks). Atomoxetine does not have the adverse effects of insomnia. Rather, fatigue and drowsiness are more common, the tolerability of which is improved with the initiation of atomoxetine at low doses with a gradual titration. The dose can also be administered in the evening to improve tolerability. Because this patient responded well to stimulant therapy with methylphenidate and there are disadvantages to atomoxetine (i.e., lower response rates and delayed onset), it would be best to manage the adverse effect of insomnia by altering the stimulant regimen (Answer D is incorrect). Administering methylphenidate OROS later in the day would probably worsen the insomnia (Answer A is incorrect). A better recommendation would be to administer methylphenidate OROS earlier in the morning, which would allow more time in the late afternoon and evening for the serum concentration to decrease before bedtime. Changing to a shorter-acting methylphenidate product (e.g., methylphenidate CD or LA) might improve the insomnia, but because of its shorter duration of action, it might compromise late-afternoon symptom control (Answer B is incorrect). In some cases, insomnia is related to rebound of ADHD symptoms when the stimulant wears off, rather than an adverse effect of the stimulant. The addition of a short-acting stimulant late in the day can help in these cases. This does not seem to apply to this patient because his late afternoon ADHD symptoms are reported to be well controlled. Counseling about proper sleep hygiene can also be an effective intervention for the management of insomnia.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

The pathogens most likely to cause pediatric sepsis or meningitis in this age group are *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* (Answer B is correct). Group B *Streptococcus*, which often colonizes the female genitourinary tract, is a common pathogen causing neonatal sepsis (Answer C is incorrect). *Pseudomonas aeruginosa* is more commonly associated with nosocomial sepsis (Answer D is incorrect). Adolescents who develop an RSV infection typically present with mild upper respiratory tract symptoms, whereas this patient's presentation suggests meningitis (Answer A is incorrect).

2. Answer: B

Before the 2014 publication of the AAP's updated guidelines, infants who were born before 31 weeks', 6 days' gestation and who were 6 months or younger at the beginning of RSV season were considered at high risk of severe infection; therefore, routine palivizumab prophylaxis was recommended solely on the basis of their prematurity. The 2014 guidelines changed the prematurity-based criteria for routine palivizumab prophylaxis to include only infants born before 29 weeks' gestation and who are younger than 12 months at the beginning of RSV season (Answer A is incorrect). According to the new guidelines, infants born between 29 and 32 weeks' gestation must have chronic lung disease to be indicated for palivizumab prophylaxis. Additionally, infants of any gestation with hemodynamically significant congenital heart disease, airway anomalies, neuromuscular disease, or who are profound immunocompromised are considered candidates for palivizumab prophylaxis (Answer B is correct). Risk factors such as day care attendance and school-aged siblings are no longer considered when determining whether prophylaxis is warranted (Answer D is incorrect). Routine prophylaxis for otherwise healthy, full-term neonates is not recommended because evidence of benefit is lacking (Answer C is incorrect).

3. Answer: C

Prophylaxis with rifampin is recommended for close contacts of patients with *N. meningitidis* or *H. influenzae* (Answer C is correct), regardless of their immunization status (Answers B and D are incorrect). Postexposure prophylaxis against pneumococcal meningitis is not recommended (Answer A is incorrect).

4. Answer: D

All scheduled immunizations should be given during the same visit. Delaying some vaccines until a later date is considered a missed opportunity (Answer A is incorrect). Oral polio vaccine is no longer recommended as part of the routine schedule because of the risk of vaccine-associated poliomyelitis, which accounts for most newly diagnosed cases in the United States since 1979 (Answer B is incorrect). Premature neonates should be vaccinated according to chronologic age, and doses should not be reduced (Answer C is incorrect). As of 2008, influenza vaccine is recommended for all children 6 months to 18 years of age during influenza season (Answer D is correct).

5. Answer: B

Otitis media is most commonly caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and viruses. Blood culture results do not predict causative organisms of otitis media (Answer A is incorrect). If the patient is older than 2 years and does not have severe symptoms (i.e., moderate to severe otalgia or body temperature of 102.2°F [39°C] or higher), delaying the decision to prescribe antibiotics is an acceptable strategy (Answer B is correct). If otalgia or fever persists for more than 48–72 hours, antibiotic therapy is acceptable, but antibiotics are not necessary if these symptoms resolve spontaneously within this time. If antibiotics are warranted and the patient does not have an allergy, high-dose amoxicillin is the treatment of choice rather than azithromycin (Answer C is incorrect). Broad-spectrum antibiotics such as ceftriaxone should be reserved for resistant cases (Answer D is incorrect).

6. Answer: D

In general, patients age 6–11 years who do not respond to one stimulant agent should be treated with a different stimulant before they are considered not to have responded to this class of drug therapy. However, switching from a methylphenidate-containing stimulant to extended-release mixed amphetamine salts (a different stimulant) should be avoided in this patient, because amphetamine-containing products have been associated with SCD in children with structural heart defects (Answer B is incorrect). The methylphenidate transdermal system has a duration of action and efficacy similar to those

of methylphenidate OROS; therefore, it is unlikely to benefit this patient because her therapy with methylphenidate immediate release and methylphenidate OROS has already failed (Answer C is incorrect). If adherence or difficulty swallowing pills were a suspected cause of treatment failure in this patient, a patch might be a reasonable alternative. Clonidine can be added as an adjunctive therapy for patients whose treatment with a single stimulant agent fails; however, it has weaker evidence than atomoxetine in this age range as the sole agent for treating ADHD (Answer A is incorrect). Atomoxetine, which is not a stimulant, would be a reasonable alternative to the stimulant class of agents in this patient, because some patients respond better to one class of agent than another (Answer D is correct).

7. Answer: A

Valproic acid is considered a first-line therapy for treating absence seizures. If the patient is having breakthrough seizures on ethosuximide—also a first-line therapy—and the dose has been maximized, it is reasonable to switch to valproic acid (Answer A is correct). Phenytoin, phenobarbital, and gabapentin have not been shown effective in treating absence seizures (Answer B, C, and D are incorrect).

8. Answer: C

	Adverse Event (loss of appetite)	
	Yes	No
Exposure (stimulant)		
Yes	7 (*a*)	193 (*b*)
No	1 (*c*)	197 (*d*)

Odds ratio = (*a*/*c*)/(*b*/*d*)
= (7/1)/(193/197)
= 7.15

9. Answer: C

A case series does not reliably establish a causal relationship, but it suggests a potential hypothesis to be studied further (Answer A is incorrect). Given the current knowledge about the potential risk of kernicterus related to ceftriaxone use, obtaining investigational review board approval for a randomized controlled or a crossover trial design would be difficult, given ethical considerations, although this study design is the gold standard for establishing a causal relationship (Answers B and D are incorrect). Therefore, a retrospective cohort would be best to investigate a causal relationship in this instance (Answer C is correct).

10. Answer: D

Patients with congenital heart defects, particularly those with hemodynamically significant lesions, are at high risk of severe RSV infection regardless of their gestational age (Answer A is incorrect). These patients are considered to be at high risk if they are younger than 12 months at the beginning of RSV season and have not undergone definitive surgical repair of their heart defect. Although this patient had surgery for his congenital heart defect, he will require another operation for complete repair (Answer C is incorrect). It is not recommended that palivizumab be initiated as routine prophylaxis in hospitalized patients because it does not reduce the incidence of nosocomial-acquired RSV infection (Answer B is incorrect). However, patients currently receiving a course of palivizumab (one dose per month for 5 months) at the time of hospital admission should have that intervention continued. In addition, cardiopulmonary bypass reduces palivizumab serum concentrations; therefore, patients undergoing congenital heart defect repair during RSV season should receive a postoperative dose of palivizumab as soon as they are medically stable, regardless of when their next scheduled dose is due (Answer D is correct).

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Group B *Streptococcus*, *Escherichia coli*, *Klebsiella* spp., and *Listeria* spp. are the most likely pathogens of neonatal sepsis or meningitis. Ampicillin plus ceftazidime administered at meningitic doses would provide reasonable empiric coverage (Answer B is correct). Ampicillin plus gentamicin is a reasonable alternative regimen. Cefotaxime or ceftazidime (when cefotaxime is unavailable) may be preferred to gentamicin because of its better penetration into the cerebrospinal fluid in meningitis caused by gram-negative organisms. In general, ceftazidime (or cefotaxime when available) use should be reserved for such cases because overuse of this agent has been associated with increased resistance and increased risk of invasive candidiasis. Although coagulase-negative *Staphylococcus* is the most likely cause of nosocomial neonatal sepsis, this patient's early presentation makes a hospital-acquired pathogen extremely unlikely. Therefore, vancomycin is unnecessary (Answer A is incorrect). Ampicillin plus ceftriaxone would provide adequate empiric antimicrobial coverage for the most likely pathogens. However, ceftriaxone use can result in biliary sludging, leading to reduced elimination of bilirubin and a potential risk of kernicterus in neonates (Answer C is incorrect). Ceftazidime plus gentamicin lacks coverage for *Listeria* and group B *Streptococcus,* which is still necessary empirically even though the mother received penicillin before delivery. In addition, empiric double-coverage of gram-negative organisms is not necessary for early onset neonatal sepsis (Answer D is incorrect).

2. Answer: C

Given this patient's age and culture results, the most likely infecting organism is *E. coli* or *Klebsiella* spp. (gram-negative rods), for which antimicrobial prophylaxis is not indicated (Answer C is correct). The most common pathogens causing meningitis in neonates do not warrant antimicrobial prophylaxis. If this patient were older and infected with *N. meningitidis* or *H. influenzae,* antibiotic prophylaxis with rifampin would be indicated for all close contacts, regardless of age or immunization status (Answers A and D are incorrect). Rifampin prophylaxis to eliminate nasal carriage is also indicated for people who receive index diagnoses of *N. meningitidis* and treatment with an antibiotic other than ceftriaxone (Answer B is incorrect).

3. Answer: C

The most likely causative organisms of sepsis or meningitis in this age group are *S. pneumoniae* and *N. meningitidis*. Therefore, a regimen of ceftriaxone plus vancomycin would provide appropriate empiric coverage (Answer C is correct). Depending on the regional incidence of resistant *S. pneumoniae,* empiric vancomycin might not be necessary. Ampicillin plus gentamicin would not provide adequate coverage (Answer A is incorrect). Cefuroxime does not provide reliable penetration into the cerebrospinal fluid; therefore, it would not be appropriate empiric coverage because this patient's presentation suggests that he has meningitis (Answer B is incorrect). Rifampin would be the drug of choice for the prophylaxis of close contacts if this patient receives a diagnosis of meningococcal meningitis; however, it is inadequate for treatment (Answer D is incorrect).

4. Answer: B

Palivizumab is the drug of choice for prophylaxis against RSV infection in high-risk patient populations, including those born before 29 weeks' gestation, regardless of risk factors, who are 12 months or younger during RSV season (Answer B is correct). Patients born between 29 and 32 weeks' gestation are not considered high risk because of their gestational age (Answer C is incorrect). To be considered as candidates for palivizumab prophylaxis, these infants must have a disease state (e.g., chronic lung disease, hemodynamically significant heart disease, airway anomalies, neuromuscular disease, profound immunodeficiency) that places them at risk of severe RSV infection. Other potential risk factors (e.g., siblings younger than 5 years or day care attenders) are no longer considered when determining the appropriateness of palivizumab prophylaxis. Patients with complex heart defects needing surgical repair are at high risk of developing severe RSV infections; however, after the repair is complete, palivizumab is no longer warranted (Answer D is incorrect). Patients with a history of chronic lung disease who are 24 months or younger and who are receiving, or have received in the past 6 months, oxygen or medical management for chronic lung disease are also at risk of severe RSV infection (Answer A is incorrect).

5. Answer: D

There is no specific treatment for RSV infection. Intravenous fluids, oxygen, and mechanical ventilation, if needed, are indicated (Answer D is correct). Palivizumab is the drug of choice for RSV prophylaxis, but it has no role in treatment (Answer A is incorrect). Corticosteroids have not been shown to be of benefit and are therefore not indicated (Answer B is incorrect). Secondary bacterial infection with *H. influenzae* or *M. catarrhalis* can occur; however, empiric antibiotic therapy is not indicated (Answer C is incorrect).

6. Answer: A

Persistence of middle ear fluid after an episode of AOM is common. If these findings are not associated with signs and symptoms of infection, a diagnosis of OME is made. The AAP practice guideline for the management of OME recommends watchful waiting (Answer A is correct). A watch-and-wait approach would not be appropriate for this patient if she were given a diagnosis of AOM rather than OME, because she is younger than 6 months. Spontaneous resolution of OME occurs within 3 months in 75%–90% of cases after AOM without residual morbidities. Children at high risk of speech and learning problems (e.g., craniofacial anomalies, Down syndrome, severe visual impairment) may need earlier, more aggressive intervention (e.g., tympanostomy tubes). Decongestants and antihistamines do not promote resolution or improve symptoms (Answer C is incorrect). Antibiotics are not effective in treating OME (Answer B is incorrect). However, high-dose amoxicillin (80–100 mg/kg/day) is considered first-line therapy for AOM. If this patient's treatment with the initial course of lower-dose amoxicillin fails (which is not a recommended regimen) or if she develops new signs of infection, then high-dose amoxicillin will be an appropriate treatment choice. Up to 74% of streptococcal strains have been reported to be resistant to azithromycin, which also has poor activity against *H. influenzae*; therefore, this would not be the best antibiotic option if an infection developed (Answer D is incorrect).

7. Answer: C

Four cases of otitis media in 12 months is considered recurrent otitis media, for which the watch-and-wait approach is not recommended (Answer D is incorrect). Previously, this patient would have been a candidate for antibiotic prophylaxis; however, this practice has fallen out of favor because of the significant risk of antimicrobial resistance compared with the minor reduction in the occurrence of otitis media (Answer A is incorrect). Tympanostomy tubes are typically reserved for patients in whom aggressive antibiotic therapy fails, and they may be effective only in otitis with bulging tympanic membrane (Answer B is incorrect). In addition, the greatest benefit of tympanostomy tubes is in patients with persistent OMEs resulting in significant hearing loss. As long as this patient continues to respond to high-dose amoxicillin, this will be considered a first-line regimen (Answer C is correct). In addition, the pneumococcal and influenza vaccines should be administered according to the recommended schedule, because these organisms are common causes of AOM.

8. Answer: D

Vaccines are often deferred for inappropriate reasons, leading to missed opportunities for immunization. Previous administration of IVIG can decrease the efficacy of live vaccines, such as MMR and varicella, but it does not affect the efficacy of inactivated products (Answer D is correct). The suggested interval between an IVIG dose and the administration of live vaccines depends on the immune globulin product and indication. Concerns about an association between MMR vaccine and the development of autism and immunizations overwhelming the immune system have been disproved by scientific evaluation (Answers A and C are incorrect). The MMR vaccine is grown in chick embryo tissue; however, an egg allergy is not a contraindication to its administration (Answer B is incorrect).

9. Answer: A

Immunocompromised patients should not receive live vaccines; therefore, the MMR and varicella vaccines should be deferred in these patients (Answer A is correct). Mild coldlike symptoms, or administration of antibiotics for mild illnesses, such as otitis media, are not a contraindication to vaccination, and deferring immunizations for such reasons is considered a missed opportunity (Answer B is incorrect). Patients with HIV, especially those with asymptomatic disease, should be considered candidates for all age-appropriate vaccines, including those containing live virus and the pneumococcal vaccine (Answer C is incorrect). Corticosteroid administration is an indication for deferral of live vaccines only if the patient is receiving high doses (more than 2 mg/kg/day of prednisone equivalent) for more than 14 days (Answer D is incorrect).

10. Answer: B

Rash associated with antiepileptic drugs is a common adverse effect, and it generally resolves within a few days after discontinuation. There is no reliable method to determine whether the rash will remain benign or progress to a more severe skin reaction; therefore, discontinuation of the offending drug is warranted (Answer D is incorrect). Carbamazepine has a higher incidence of rash than oxcarbazepine does, and cross-reactivity has been noted (Answer A is incorrect). Valproic acid is a good choice for managing focal seizures, and it has a low incidence of rash. However, the principal adverse effects of valproic acid include weight gain and menstrual irregularities, both of which would be undesirable in this overweight teenager. In addition, valproic acid is a known teratogen (pregnancy category D) that should be avoided if other options are available in girls of reproductive age who are unreliable in their use of contraception (Answer C is incorrect). Levetiracetam (pregnancy category C) has a low incidence of rash and minimal drug interactions (Answer B is correct).

11. Answer: A

Stimulants, especially methylphenidate, are generally considered first-line therapy for treating ADHD. Because this patient shows symptoms at school and at home, the short duration of action (3–5 hours) of a twice-daily methylphenidate immediate-release regimen will probably not provide adequate symptom relief (Answer B is incorrect). Likewise, D-methylphenidate has a short duration of action. In addition, D-methylphenidate is no more effective and has no fewer adverse effects than methylphenidate immediate release. Therefore, D-methylphenidate is generally not considered cost-effective (Answer D is incorrect). Extended-release guanfacine was recently approved by the FDA for the treatment of ADHD, but it should be reserved for patients with ADHD and tic disorders or those who have not responded to stimulant agents (Answer C is incorrect). Methylphenidate (OROS) with its longer duration of action (10–12 hours) would provide the best coverage (Answer A is correct). Therapy with this drug can be initiated without previous titration using methylphenidate immediate release.

12. Answer: C

Changing to a methylphenidate transdermal patch allows flexibility in the duration of drug effect. Wearing the patch for 9 hours results in about 12 hours of therapeutic effect; however, the patch can be removed sooner, thus reducing the duration of effect and allowing serum concentrations to decrease before bedtime (Answer C is correct). Response rates to atomoxetine are lower than to methylphenidate (OROS) in children with ADHD. In addition, the onset of therapeutic effect for atomoxetine is delayed (typically 2–4 weeks). Atomoxetine does not have the adverse effects of insomnia. Rather, fatigue and drowsiness are more common, the tolerability of which is improved with the initiation of atomoxetine at low doses with a gradual titration. The dose can also be administered in the evening to improve tolerability. Because this patient responded well to stimulant therapy with methylphenidate and there are disadvantages to atomoxetine (i.e., lower response rates and delayed onset), it would be best to manage the adverse effect of insomnia by altering the stimulant regimen (Answer D is incorrect). Administering methylphenidate OROS later in the day would probably worsen the insomnia (Answer A is incorrect). A better recommendation would be to administer methylphenidate OROS earlier in the morning, which would allow more time in the late afternoon and evening for the serum concentration to decrease before bedtime. Changing to a shorter-acting methylphenidate product (e.g., methylphenidate CD or LA) might improve the insomnia, but because of its shorter duration of action, it might compromise late-afternoon symptom control (Answer B is incorrect). In some cases, insomnia is related to rebound of ADHD symptoms when the stimulant wears off, rather than an adverse effect of the stimulant. The addition of a short-acting stimulant late in the day can help in these cases. This does not seem to apply to this patient because his late afternoon ADHD symptoms are reported to be well controlled. Counseling about proper sleep hygiene can also be an effective intervention for the management of insomnia.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
The pathogens most likely to cause pediatric sepsis or meningitis in this age group are *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* (Answer B is correct). Group B *Streptococcus*, which often colonizes the female genitourinary tract, is a common pathogen causing neonatal sepsis (Answer C is incorrect). *Pseudomonas aeruginosa* is more commonly associated with nosocomial sepsis (Answer D is incorrect). Adolescents who develop an RSV infection typically present with mild upper respiratory tract symptoms, whereas this patient's presentation suggests meningitis (Answer A is incorrect).

2. Answer: B
Before the 2014 publication of the AAP's updated guidelines, infants who were born before 31 weeks', 6 days' gestation and who were 6 months or younger at the beginning of RSV season were considered at high risk of severe infection; therefore, routine palivizumab prophylaxis was recommended solely on the basis of their prematurity. The 2014 guidelines changed the prematurity-based criteria for routine palivizumab prophylaxis to include only infants born before 29 weeks' gestation and who are younger than 12 months at the beginning of RSV season (Answer A is incorrect). According to the new guidelines, infants born between 29 and 32 weeks' gestation must have chronic lung disease to be indicated for palivizumab prophylaxis. Additionally, infants of any gestation with hemodynamically significant congenital heart disease, airway anomalies, neuromuscular disease, or who are profound immunocompromised are considered candidates for palivizumab prophylaxis (Answer B is correct). Risk factors such as day care attendance and school-aged siblings are no longer considered when determining whether prophylaxis is warranted (Answer D is incorrect). Routine prophylaxis for otherwise healthy, full-term neonates is not recommended because evidence of benefit is lacking (Answer C is incorrect).

3. Answer: C
Prophylaxis with rifampin is recommended for close contacts of patients with *N. meningitidis* or *H. influenzae* (Answer C is correct), regardless of their immunization status (Answers B and D are incorrect). Postexposure prophylaxis against pneumococcal meningitis is not recommended (Answer A is incorrect).

4. Answer: D
All scheduled immunizations should be given during the same visit. Delaying some vaccines until a later date is considered a missed opportunity (Answer A is incorrect). Oral polio vaccine is no longer recommended as part of the routine schedule because of the risk of vaccine-associated poliomyelitis, which accounts for most newly diagnosed cases in the United States since 1979 (Answer B is incorrect). Premature neonates should be vaccinated according to chronologic age, and doses should not be reduced (Answer C is incorrect). As of 2008, influenza vaccine is recommended for all children 6 months to 18 years of age during influenza season (Answer D is correct).

5. Answer: B
Otitis media is most commonly caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and viruses. Blood culture results do not predict causative organisms of otitis media (Answer A is incorrect). If the patient is older than 2 years and does not have severe symptoms (i.e., moderate to severe otalgia or body temperature of 102.2°F [39°C] or higher), delaying the decision to prescribe antibiotics is an acceptable strategy (Answer B is correct). If otalgia or fever persists for more than 48–72 hours, antibiotic therapy is acceptable, but antibiotics are not necessary if these symptoms resolve spontaneously within this time. If antibiotics are warranted and the patient does not have an allergy, high-dose amoxicillin is the treatment of choice rather than azithromycin (Answer C is incorrect). Broad-spectrum antibiotics such as ceftriaxone should be reserved for resistant cases (Answer D is incorrect).

6. Answer: D
In general, patients who do not respond to one stimulant agent should be treated with a different stimulant before they are considered not to have responded to this class of drug therapy. However, switching from a methylphenidate-containing stimulant to extended-release mixed amphetamine salts (a different stimulant) should be avoided in this patient, because amphetamine-containing products have been associated with SCD in children with structural heart defects (Answer B is incorrect). The methylphenidate transdermal system

has a duration of action and efficacy similar to those of methylphenidate OROS; therefore, it is unlikely to benefit this patient because her therapy with methylphenidate immediate release and methylphenidate OROS has already failed (Answer C is incorrect). If adherence or difficulty swallowing pills were a suspected cause of treatment failure in this patient, a patch might be a reasonable alternative. Clonidine can be added as an adjunctive therapy for patients whose treatment with a single stimulant agent fails; however, it should not be used as the sole agent for treating ADHD (Answer A is incorrect). Atomoxetine, which is not a stimulant, would be a reasonable alternative to the stimulant class of agents in this patient, because some patients respond better to one class of agent than another (Answer D is correct).

7. Answer: A

Valproic acid is considered a first-line therapy for treating absence seizures. If the patient is having breakthrough seizures on ethosuximide—also a first-line therapy—and the dose has been maximized, it is reasonable to switch to valproic acid (Answer A is correct). Phenytoin, phenobarbital, and gabapentin have not been shown effective in treating absence seizures (Answer B, C, and D are incorrect).

8. Answer: C

	Adverse Event (loss of appetite)	
	Yes	No
Exposure (stimulant)		
Yes	7 (*a*)	193 (*b*)
No	1 (*c*)	197 (*d*)

Odds ratio = (*a*/*c*)/(*b*/*d*)
= (7/1)/(193/197)
= 7.15

9. Answer: C

A case series does not reliably establish a causal relationship, but it suggests a potential hypothesis to be studied further (Answer A is incorrect). Given the current knowledge about the potential risk of kernicterus related to ceftriaxone use, obtaining investigational review board approval for a randomized controlled or a crossover trial design would be difficult, given ethical considerations, although this study design is the gold standard for establishing a causal relationship (Answers B and D are incorrect). Therefore, a retrospective cohort would be best to investigate a causal relationship in this instance (Answer C is correct).

10. Answer: D

Patients with congenital heart defects, particularly those with hemodynamically significant lesions, are at high risk of severe RSV infection regardless of their gestational age (Answer A is incorrect). These patients are considered to be at high risk if they are younger than 12 months at the beginning of RSV season and have not undergone definitive surgical repair of their heart defect. Although this patient had surgery for his congenital heart defect, he will require another operation for complete repair (Answer C is incorrect). It is not recommended that palivizumab be initiated as routine prophylaxis in hospitalized patients because it does not reduce the incidence of nosocomial-acquired RSV infection (Answer B is incorrect). However, patients currently receiving a course of palivizumab (one dose per month for 5 months) at the time of hospital admission should have that intervention continued. In addition, cardiopulmonary bypass reduces palivizumab serum concentrations; therefore, patients undergoing congenital heart defect repair during RSV season should receive a postoperative dose of palivizumab as soon as they are medically stable, regardless of when their next scheduled dose is due (Answer D is correct).

Biostatistics: A Refresher

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Biostatistics: A Refresher

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Learning Objectives

1. Review different types of statistics (inferential and descriptive) and data (nominal, ordinal, continuous [ratio and interval]) to determine an appropriate type of statistical test on the basis of the sample distribution, data type, and study design.
2. Review different types of measures of central tendency (mean, median, and mode) and data spread (standard deviation, standard error of the mean, range, and interquartile range).
3. Interpret hypothesis testing, decision errors, p values, confidence intervals, and statistical and clinical significance.
4. Interpret the similarities and differences between statistical tests used to compare two or more groups for appropriate use.
5. Interpret the similarities and differences between regression, correlation, and survival analyses for appropriate use.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of the chapter.

1. A randomized controlled trial assesses the effects of the treatment of heart failure on global functioning in three groups of adults after 6 months of treatment. Investigators wanted to assess global functioning with the New York Heart Association (NYHA) functional classification, an ordered scale from I to IV, and to compare the patient classification after 6 months of treatment. Which statistical test is most appropriate to assess differences in functional classification between the groups?
   A. Kruskal-Wallis test.
   B. Wilcoxon signed-rank test.
   C. Analysis of variance (ANOVA).
   D. Analysis of covariance (ANCOVA).

2. You are evaluating a randomized, double-blind, parallel-group controlled trial that compares four antihypertensive drugs for their effect on blood pressure. The authors conclude that hydrochlorothiazide is better than atenolol ($p<0.05$) and that enalapril is better than hydrochlorothiazide ($p<0.01$), but no difference is observed between any other drugs. The investigators used an unpaired (independent samples) t-test to test the hypothesis that each drug was equal to the other. Which statement is most appropriate?
   A. Investigators used the appropriate statistical test to analyze their data.
   B. Enalapril is the most effective of these drugs.
   C. ANOVA is a more appropriate test.
   D. A paired t-test is a more appropriate test.

3. In the results of a randomized, double-blind, controlled clinical trial, the difference in hospital readmission rates between the intervention group and the control group is 6% ($p=0.01$), and it is concluded that there is a statistically significant difference between the groups. Which statement is most consistent with this finding and conclusions?
   A. The chance of making a type I error is 5 in 100.
   B. The trial does not have enough power.
   C. There is a high likelihood of having made a type II error.
   D. The chance of making a type I error is 1 in 100.

4. You are reading a manuscript that evaluates the impact of obesity on enoxaparin pharmacokinetics. The authors used an unpaired t-test to compare the baseline values of body mass index (BMI) in normal subjects and obese subjects. You are evaluating the use of an unpaired t-test to compare the BMI between the two groups. Which choice best represents the most appropriate criteria to be met to use this parametric test?
   A. The sample sizes in the normal and obese subjects should be equal to allow the use of a t-test.
   B. A t-test is not appropriate because BMI data are ordinal.
   C. The variance of the BMI data has to be similar in each group.
   D. The pre-study power should be at least 90%.

5. You are evaluating the results and discussion of a journal club article to present to the pharmacy residents at your institution. The randomized, prospective, controlled trial evaluated the efficacy of a new controller drug for asthma. The primary end point was the morning forced expiratory volume

in 1 second (FEV_1) in two groups of subjects (men and women). The difference in FEV_1 between the two groups was 15% (95% confidence interval [CI], 10%–21%). Which statement is most appropriate, given the results?

A. Without the reporting of a p-value, it is not possible to conclude whether these results were statistically significant.

B. There is a statistically significant difference between the men and women ($p<0.05$).

C. There is a statistically significant difference between the men and women ($p<0.01$).

D. There is no statistically significant difference between the men and women.

6. An early-phase clinical trial of 40 subjects evaluated a new drug known to increase high-density lipoprotein cholesterol (HDL) concentrations. The objective of the trial was to compare the new drug's ability to increase HDL with that of lifestyle modifications (active control group). At the beginning of the study, the mean baseline HDL was 37 mg/dL in the active control group and 38 mg/dL in the new drug group. At the end of the 3-month trial, the mean HDL for the control group was 44 mg/dL and for the new drug group, 49 mg/dL. The p-value for the comparison at 3 months was 0.08. Which statement provides the best interpretation of these results?

A. An a priori α of less than 0.10 would have made the study more clinically useful.

B. The new drug and active control appear to be equally efficacious in increasing HDL concentrations.

C. The new drug is better than lifestyle modifications because it increases HDL concentrations to a greater extent.

D. This study is potentially underpowered.

7. Researchers planned a study to evaluate the percentage of subjects who achieved less than a target blood pressure (less than 140/90 mm Hg) when initiating therapy with two different doses of amlodipine. In the study of 100 subjects, the amlodipine 5-mg group (n=50) and the amlodipine 10-mg group (n=50) were compared. The investigators used a blood pressure goal as their primary end point, defined as the percentage of subjects who successfully achieved the blood pressure goal at 3 months. Which is the most appropriate statistical test to answer such a question?

A. Independent samples t-test.

B. Chi-square or Fisher's exact test.

C. Wilcoxon signed-rank test.

D. One-sample t-test.

8. An investigational drug is being compared with an existing drug for the treatment of anemia in patients with chronic kidney disease. The study is designed to detect a minimum 20% difference in response rates between the groups, if one exists, with an a priori α of 0.05 or less. The investigators are unclear whether the 20% difference between response rates is too large and think a smaller difference might be more clinically meaningful. In revising their study, they decide they want to be able to detect a minimum 10% difference in response. Which change to the study parameters is most appropriate?

A. Increase the sample size.

B. Select an α of 0.001 as a cutoff for statistical significance.

C. Select an α of 0.10 as a cutoff for statistical significance.

D. Decrease the sample size.

9. You are designing a new computer alert system to investigate the impact of several factors on the risk of corrected QT interval (QTc) prolongation. You want to develop a model to predict which patients are most likely to experience QTc prolongation after the administration of certain drugs or the presence of certain conditions. You plan to assess the presence or absence of several different variables. Which technique will be most useful in completing such an analysis?

A. Correlation.

B. Kaplan-Meier curve.

C. Regression.

D. Confidence intervals.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

2. Application of Evidence to Practice and Education
    a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Sub-task(s): 2.1.2
    b. 2.2. Evaluate pharmacotherapy-related literature and health information. Sub-task(s): 2.2.1, 2.2.2, 2.2.5, 2.2.7, 2.2.9, 2.2.12

I. INTRODUCTION TO STATISTICS

A. Statistics allow us to classify, summarize, and analyze data.

B. Statistics enable investigators to summarize data, determine the likelihood that a treatment or procedure will affect a group of patients, and estimate the effect size.

C. Statistics help us determine whether the results of a study can be applied to our practice.

D. Why Pharmacists Need to Know Statistics

E. As Statistics Pertains to Most of You
   1. Pharmacotherapy Specialty Examination content outline, Domain 2: Application of Evidence to Practice and Education (25%)
   2. Task statements:
      a. Retrieve relevant information that addresses pharmacotherapy-related inquiries.
      b. Evaluate pharmacotherapy-related literature, and health information.
      c. Disseminate pharmacotherapy-related information to educate health care professionals, patients, and caregivers.

F. Examples of Online Statistical and Study Design Tools
   1. www.graphpad.com/quickcalcs/
   2. http://statpages.org/

G. Several papers have investigated the various types of statistical tests used in the biomedical literature.

Table 1. Statistical Content of Original Articles in *New England Journal of Medicine*, 2004–2005

Statistical Test/Procedure	%	Statistical Test/Procedure	%
No statistics or descriptive statistics	13	Adjustment and standardization	1
t-tests	26	Multiway tables	13
Contingency tables	53	Power analyses	39
Nonparametric tests	27	Cost-benefit analysis	< 1
Epidemiologic statistics	35	Sensitivity analysis	6
Pearson correlation	3	Repeated-measures analysis	12
Simple linear regression	6	Missing-data methods	8
Analysis of variance	16	Noninferiority trials	4
Transformation	10	Receiver operating characteristics	2
Nonparametric correlation	5	Resampling	2
Survival methods	61	Principal component and cluster analyses	2
Multiple regression	51	Other methods	4
Multiple comparisons	23		

[a]Only applies to articles with Methods.

Table 2. Statistical Content of Original Articles from Six Major Medical Journals from January to March 2005 (n=239 articles)[a]

Statistical Test/Procedure	No. (%)	Statistical Test/Procedure	No. (%)
Descriptive statistics (mean, median, frequency, SD, and IQR)	219 (92)	Others	
Simple statistics	120 (50)	Intention-to-treat analysis	42 (17.6)
Chi-square analysis	70 (29)	Incidence or prevalence	39 (16.3)
t-test	48 (20)	Relative risk or risk ratio	29 (12.2)
Kaplan-Meier analysis	48 (20)	Sensitivity analysis	21 (8.8)
Wilcoxon rank sum test	38 (16)	Sensitivity or specificity	15 (6.3)
Fisher's exact test	33 (14)		
Analysis of variance	21 (9)		
Correlation	16 (7)		
Multivariate analysis	164 (69)		
Cox proportional hazards	64 (27)		
Multiple logistic regression	54 (23)		
Multiple linear regression	7 (3)		
Other regression analysis	38 (16)		
None	5 (2)		

[a]Articles published in *American Journal of Medicine*, *Annals of Internal Medicine*, *BMJ*, *Journal of the American Medical Association*, *Lancet*, and *New England Journal of Medicine*.

IQR = interquartile range; SD = standard deviation.

Source of data in Tables 1 and 2: Horton NJ, Switzer S. Statistical methods in the Journal, N Engl J Med 2005;353:1977-9; Windish DM, Huot SJ, Green ML. Medicine resident's understanding of the biostatistics and results in the medical literature, JAMA 2007;298:1010-22.

II. TYPES OF VARIABLES AND DATA

A. Definition: Random Variables—A variable with observed values that may be considered outcomes of an experiment and whose values cannot be anticipated with certainty before the experiment is conducted

B. Two Types of Random Variables
   1. Qualitative variables
   2. Quantitative variables

C. Qualitative variables
   1. Can take only a limited number of values within a given range
   2. Often referred to as categorical variables
   3. Nominal: Classified into groups in an unordered manner and with no indication of relative severity (e.g., mortality [dead or alive], disease presence [yes or no], race, marital status)
   4. Ordinal: Ranked in a specific order but with no consistent level of magnitude of difference between ranks (e.g., NYHA functional class describes the functional status of patients with heart failure, and subjects are classified in increasing order of symptoms: I, II, III, IV; Likert-type scales [strongly agree {SA}, agree {A}, neutral {N}, disagree {D}, strongly disagree {SD}; disease stages [A, B, C, D])
      a. These are not real numbers.
      b. Common error: Measure of central tendency – in most cases, means and standard deviations (SDs) – should not be reported with ordinal data.

D. Quantitative Variables
   1. Discrete quantitative variables can take specific numeric values (1, 2, 3, 4, etc.), rather than any value in an interval as described for continues below. These numeric values have a clear quantitative value (number of hospitalizations, number of pregnancies)
   2. Quantitative continuous variables can take on any value within a given range.
      a. Interval: Data are ranked in a specific order with a consistent change in magnitude between units; the zero point is arbitrary (e.g., degrees Fahrenheit).
      b. Ratio: Like "interval" but with an absolute zero (e.g., degrees Kelvin, heart rate, blood pressure, time, distance)

III. TYPES OF STATISTICS

A. Descriptive Statistics: Used to summarize and describe data that are collected or generated in research studies. This is done both visually and numerically.
   1. Visual methods of describing data
      a. Frequency distribution
      b. Histogram
      c. Scatterplot
      d. Boxplot
   2. Numerical methods of describing data: Measures of central tendency
      a. Arithmetic mean (i.e., average)
         i. Sum of all values divided by the total number of values
         ii. Should generally be used only for continuous and normally distributed data
         iii. Very sensitive to outliers and tend toward the tail, which has the outliers
         iv. Most commonly used and most understood measure of central tendency
         v. Geometric mean: Useful for data that have log-normal distributions
      b. Median
         i. Midpoint of the values when placed in order from highest to lowest. Half of the observations are above and half are below. When there is an even number of observations, it is the mean of the two middle values.
         ii. Also called 50th percentile
         iii. Can be used for ordinal or continuous data (especially good for skewed populations)
         iv. Insensitive to outliers
      c. Mode
         i. Most common value in a distribution
         ii. Can be used for nominal, ordinal, or continuous data
         iii. Sometimes, there may be more than one mode (e.g., bimodal, trimodal).
         iv. Does not help describe meaningful distributions with a large range of values, each of which occurs infrequently
   3. Numerical methods of describing data: Measures of data spread or variability
      a. Standard deviation
         i. Measure of the variability about the mean; most common measure used to describe the spread of data
         ii. Square root of the variance (average squared difference of each observation from the mean); returns variance back to original units (non-squared)
         iii. Appropriately applied only to continuous data that are normally or near normally distributed or that can be transformed to be normally distributed

iv. By the empirical rule for normal distributions, 68% of the sample values are found within ±1 SD, 95% are found within ±2 SD, and 99% are found within ±3 SD.
v. The coefficient of variation relates the mean and the SD (SD/mean × 100%).

b. Range
i. Difference between the smallest and largest values in a data set does not give a tremendous amount of information by itself.
ii. Easy to compute (simple subtraction)
iii. Size of range is very sensitive to outliers.
iv. Often reported as the actual values rather than the difference between the two extreme values

c. Percentiles
i. The point (value) in a distribution in which a value is larger than some percentage of the other values in the sample. Can be calculated by ranking all data in a data set
ii. The 75th percentile lies at a point at which 75% of the other values are smaller.
iii. Does not assume the population has a normal distribution (or any other distribution)
iv. The interquartile range (IQR) is an example of the use of percentiles to describe the middle 50% values. The IQR encompasses the 25th–75th percentile.

4. Presenting data using only measures of central tendency can be misleading without some idea of data spread. Studies that report only medians or means without their accompanying measures of data spread should be closely scrutinized. What are the measures of spread that should be used with means and medians?
5. Example data set (Table 3)

Table 3. Twenty Baseline HDL Concentrations from an Experiment Evaluating the Impact of Green Tea on HDL

64	60	59	65	64	62	54
54	68	67	79	55	48	65
59	65	87	49	46	46	

a. Calculate the mean, median, and mode of the data set given in Table 3.
b. Calculate the range, and SD (on examination, you will most likely not have to do this by hand).
c. Which figure(s) would allow us to evaluate the visual presentation of the data?

B. Inferential Statistics
1. Conclusions or generalizations made about a population (large group) from the study of a sample of that population
2. Choosing and evaluating statistical methods depend, in part, on the type of data used.
3. An educated statement about an unknown population is commonly called an inference in statistics.
4. Statistical inference can be made by estimation or hypothesis testing.

IV. POPULATION DISTRIBUTIONS

A. Discrete Distributions
1. Binomial distribution: There are two possible outcomes; the probability of obtaining either outcome is known, and you want to know the chance of observing a certain number of successes in a certain number of trials.
2. Poisson distribution: Counting events in a certain period of observation: The average number of counts is known, and you want to know the likelihood of observing a various number of events.

B. Normal (Gaussian) Distribution
   1. Most common model for population distributions
   2. Symmetric or bell-shaped frequency distribution
   3. Landmarks for continuous, normally distributed data
      a. μ: Population mean is equal to zero.
      b. σ: Population SD is equal to 1.
      c. $\bar{x}$ and s: These represent the sample mean and SD.
   4. When a random variable is measured in a large enough sample of any population, some values will occur more often than will others.
   5. A visual check of a distribution can help determine whether it is normally distributed (whether it appears symmetric and bell shaped). Need the data to perform these checks.
      a. Frequency distribution and histograms (visually look at the data)
      b. Median and mean will be about equal for normally distributed data (most practical and easiest to use).
      c. Formal test: Kolmogorov-Smirnov test and others
      d. More challenging to evaluate this when we do not have access to the data (when we are reading an article), because most articles do not present all data or both the mean and median
   6. The parameters mean and SD define a normally distributed population.
   7. Probability: The likelihood that any one event will occur given all the possible outcomes
   8. Estimation and sampling variability
      a. Estimation is one method that can be used to make an inference about a population parameter
      b. Separate samples (even of the same size) from a single population will give slightly different estimates.
      c. The distribution of means from random samples approximates a normal distribution.
         i. The mean of this "distribution of means" is equal to the unknown population mean, μ.
         ii. The SD of the means is estimated by the standard error of the mean (SEM).
         iii. As in any normal distribution, 95% of the sample means lie within ±2 SEM of the population mean.
      d. The distribution of means from these random samples is about normal regardless of the underlying population distribution (central limit theorem). You will get slightly different mean and SD values each time you repeat this experiment.
      e. The SEM is estimated with a single sample by dividing the SD by the square root of the sample size (n). The SEM quantifies uncertainty in the estimate of the mean, not variability in the sample. Important for hypothesis testing and 95% CI estimation
      f. Why is all this information about the difference between the SEM and SD worth knowing?
         i. Calculation of CIs (95% CI is approximately the mean ± 2 times the SEM.)
         ii. Hypothesis testing
         iii. Deception (e.g., makes results look less "variable," especially when used in graphic format)
   9. Recall the previous example about HDL and green tea. From the calculated values in section III, do these data appear to be normally distributed?

V. CONFIDENCE INTERVALS

A. Commonly Reported as a Way to Estimate a Population Parameter
   1. In the medical literature, 95% CIs are the most commonly reported CIs. In repeated samples, 95% of all CIs include true population value (i.e., the likelihood [or probability] that the population value is contained within the interval). In some cases, 90% or 99% CIs are reported. Why are 95% CIs most often reported?

2. Example
    a. Assume a baseline birth weight in a group (n=51) with a mean ± SD of 1.18 ± 0.4 kg.
    b. 95% CI is about equal to the mean ± 1.96 × SEM (or 2 × SEM). In reality, it depends on the distribution being used and is a bit more complicated.
    c. What is the 95% CI? The 95% CI is calculated to be (1.07, 1.29), meaning there is 95% certainty that the true mean of the entire population studied will be 1.07–1.29 kg.
    d. What is the 90% CI? The 90% CI is calculated to be (1.09, 1.27). The 95% CI will always be wider than the 90% CI for any given sample. Therefore, the wider the CI, the more likely it is to encompass the true population mean.
3. The differences between the SD, SEM, and CIs should be noted when interpreting the literature because they are often used interchangeably. Although it is common for CIs to be confused with SDs, the information each provides is quite different and has to be assessed correctly.
4. Recall the previous example about HDL and green tea. What is the 95% CI of the data set, and what does that mean?

B. CIs can also be used for any sample estimate. Estimates derived from categorical data such as risk, risk differences, and risk ratios are often presented with the CI and will be discussed in the text that follows.

VI. HYPOTHESIS TESTING

A. Null and Alternative Hypotheses (see Table 4 for other types of examples)
1. Null hypothesis (H_0): Example: No difference between groups being compared (treatment A equals treatment B)
2. Alternative hypothesis (H_A): Example: Opposite of null hypothesis; states that there is a difference (treatment A does not equal treatment B)
3. The structure or the manner in which the hypothesis is written dictates which statistical test is used. Two-sample t-test: H_0: Mean 1 = Mean 2
4. Used to assist in determining whether any observed differences between groups can be explained by chance
5. Tests for statistical significance (hypothesis testing) determine whether the data are consistent with H_0 (no difference).
6. The results of the hypothesis testing will indicate whether enough evidence exists for H_0 to be rejected.
    a. If H_0 is rejected: Statistically significant difference between groups (unlikely attributable to chance)
    b. If H_0 is not rejected: No statistically significant difference between groups (any apparent differences may be attributable to chance). Note that we are not concluding that the treatments are equal.
7. Types of hypothesis testing. These are situations in which two groups are being compared. There are numerous other examples of situations these procedures could be applied to (Table 4).

Table 4. Types of Hypothesis Testing

	Question	Hypothesis	Method
Nondirectional			
Difference	Are the means different?	H_0: $Mean_1 = Mean_2$ H_A: $Mean_1 \neq Mean_2$ or H_0: $Mean_1 - Mean_2 = 0$ H_A: $Mean_1 - Mean_2 \neq 0$	Traditional 2-sided t-test Confidence intervals
Equivalence	Are the means practically equivalent?	H_0: $Mean_1 - Mean_2 \geq \Delta$ H_A: $Mean_1 - Mean_2 < \Delta$	Two 1-sided t-test (TOST) procedure Confidence intervals
Directional			
Superiority	Is mean 1 > mean 2? (or some other similarly worded question)	H_0: $Mean_1 \leq Mean_2$ H_A: $Mean_1 > Mean_2$ or H_0: $Mean_1 - Mean_2 \leq 0$ H_A: $Mean_1 - Mean_2 > 0$	Traditional 1-sided t-test Confidence intervals
Noninferiority	Is mean 1 no more than a certain amount lower than mean 2?	H_0: $Mean_1 - Mean_2 \geq \Delta$ H_A: $Mean_1 - Mean_2 < \Delta$	Confidence intervals

Δ = equivalence or noninferiority margin; H_0 = null hypothesis; H_A = alternative hypothesis.

B. To Determine What Is Sufficient Evidence to Reject H_0: Set the a priori significance level (α) and generate the decision rule.
   1. Developed after the research question has been stated in hypothesis form
   2. Used to determine the level of acceptable error caused by a false positive (also known as level of significance)
      a. Convention: A priori α is usually 0.05.
      b. Critical value is calculated, capturing how extreme the sample data must be to reject H_0.

C. Perform the Experiment and Estimate the Test Statistic.
   1. A test statistic is calculated from the observed data in the study, which is compared with the critical value.
   2. Depending on this test statistic's value, H_0 is not rejected (often called fail to reject) or rejected.
   3. In general, the test statistic and critical value are not presented in the literature; instead, p-values are generally reported and compared with a priori α values to assess statistical significance. p-value: Probability of obtaining a test statistic and critical value as extreme as or more extreme than the one actually obtained
   4. Because computers are used in these tests, this step is often transparent; the p-value estimated in the statistical test is compared with the a priori α (usually 0.05), and the decision is made.

D. CIs Instead of Hypothesis Testing
   1. Hypothesis testing and calculation of p values tell us (ideally) whether there is a statistically significant difference between groups, but nothing about the magnitude of the difference.
   2. CIs help us determine the importance of a finding or findings, which we can apply to a situation.
   3. CIs give us an idea of the magnitude of the difference between groups and the statistical significance.
   4. CIs are a range of data, together with a point estimate of the difference.

5. Wide CIs
    a. Many results are possible, either larger or smaller than the point estimate provided by the study.
    b. All values contained in the CI are statistically plausible.
6. If the estimate is the difference between two continuous variables: A CI that includes zero (no difference between two variables) can be interpreted as not statistically significant (a p value of 0.05 or greater). There is no need to show both the 95% CI and the p value.
7. The interpretation of CIs for odds ratios and relative risks is somewhat different. In this case, a value of 1 indicates no difference in risk, and if the CI includes 1, there is no statistical difference. (See the discussion of case-control/cohort studies in other sections for how to interpret CIs for odds ratios and relative risks.)
8. There is no need to report both the 95% CI and the p value.

VII. DECISION ERRORS

Table 5. Summary of Decision Errors

	Underlying Truth or Reality	
Test Result	H_0 is true (no difference)	H_0 is false (difference)
Accept H_0 (no difference)	No error (correct decision)	Type II error (β error)
Reject H_0 (difference)	Type I error (α error)	No error (correct decision)

H_0 = null hypothesis.

A. Type I error: The probability of making this error is defined as the significance level α.
    1. Convention is to set the α to 0.05, effectively meaning that, 1 in 20 times, a type I error will occur when the H_0 is rejected. Thus, 5.0% of the time, a researcher will conclude that there is a statistically significant difference when one does not actually exist.
    2. The calculated chance that a type I error has occurred is called the p-value.
    3. The p-value tells us the likelihood of obtaining a given (or a more extreme) test result if the H_0 is true. When the α level is set a priori, H_0 is rejected when p is less than α. In other words, the p-value tells us the probability of being wrong when we conclude that a true difference exists (false positive).
    4. A lower p-value does not mean the result is more important or more meaningful, but only that it is statistically significant and not likely to be attributable to chance.

B. Type II error: The probability of making this error is called β.
    1. Concluding that no difference exists when one truly does (not rejecting H_0 when it should be rejected)
    2. It has become a convention to set β at 0.10–0.20.

C. Power ($1 - \beta$)
    1. The probability of making a correct decision when H_0 is false; the ability to detect differences between groups if one actually exists
    2. Dependent on the following factors:
        a. Predetermined α
        b. Sample size
        c. The size of the difference between the outcomes you want to detect: Often not known before conducting the experiment, so to estimate the power of your test, you will have to specify how large a change is worth detecting (usually determined from previous data the investigator has or from the literature)
        d. The variability of the outcomes that are being measured (usually determined from previous data the investigator has or from the literature)

e. Power is decreased by poor study design and/or the use of incorrect statistical tests (use of nonparametric tests when parametric tests are appropriate).

3. Statistical power analysis and sample size calculation
   a. Related to the previous discussion of power and sample size
   b. Sample size estimates should be performed in all studies a priori.
   c. Necessary components for estimating appropriate sample size
      i. Acceptable type II error rate (usually 0.10–0.20)
      ii. Observed difference in predicted study outcomes that is clinically significant
      iii. The expected variability in item ii
      iv. Acceptable type I error rate (usually 0.05)
      v. Statistical test that will be used for primary end point
4. Statistical significance versus clinical significance
   a. As stated earlier, the size of the p-value is not necessarily related to the clinical importance of the result. Smaller values mean only that chance is less likely to explain observed differences.
   b. Statistically significant does not necessarily mean clinically significant.
   c. Lack of statistical significance does not mean that results are not clinically important.
   d. When considering nonsignificant findings, consider sample size, estimated power, and observed variability.

Table 6. Four Studies Carried Out to Test the Response Rate to a New Drug vs. That to a Standard Drug

		Difference in % Responding			
Study	**New Drug Response Rate (%)**	**New Drug Response Rate (%)**	**p Value**	**Point Estimate (%)**	**95% CI**
1	480 of 800 (60)	416 of 800 (52)	0.001	8	3%–13%
2	15 of 25 (60)	13 of 25 (52)	0.57	8	-19% to 35%
3	15 of 25 (60)	9 of 25 (36)	0.09	24	-3% to 51%
4	240 of 400 (60)	144 of 400 (36)	<0.0001	24	17%–31%

   e. Which study (or studies) observed a statistically significant difference in response rate?
   f. If the smallest change in response rate thought to be clinically significant is 15%, which of these trials may be convincing enough to change your practice?

VIII. STATISTICAL TESTS AND CHOOSING A STATISTICAL TEST

A. Basic Study Designs
   1. Number of study groups or samples
      a. One
      b. Two
      c. More than two
   2. Related samples (paired or matched)
      a. Crossover design
      b. Two or more observations in the same biologic unit
   3. Independent samples
      a. Parallel design
      b. Different people in each group or sample
      c. Less statistical efficiency than crossover design

B. Choosing the Appropriate Statistical Test Depends on the Following:
   1. Type of data (e.g., qualitative [nominal, ordinal] vs. quantitative [continuous])
   2. Distribution and/or spread of data (e.g., normal vs. nonnormal)
   3. Number of groups
   4. Study design (e.g., parallel, crossover)

C. Parametric vs. Nonparametric Tests
   1. Parametric tests assume the following:
      a. Data being investigated have an underlying distribution that is normal or close to normal or, more correctly, randomly drawn from a parent population with a normal distribution. Remember how to estimate this (mean ~ median)?
      b. Data measured are quantitative continuous data measured on either an interval or a ratio scale.
      c. Parametric tests assume that the data being investigated have variances that are homogeneous between the groups investigated. This is often called homoscedasticity.

   2. Nonparametric tests
      a. "Distribution-free" statistics
      b. Data are not (or do not need to be) normally distributed. Skewed quantitative continuous data
      c. Data do not meet other criteria; quantitative discrete, ordinal, or nominal data

D. Examples of Representative Statistical Tests

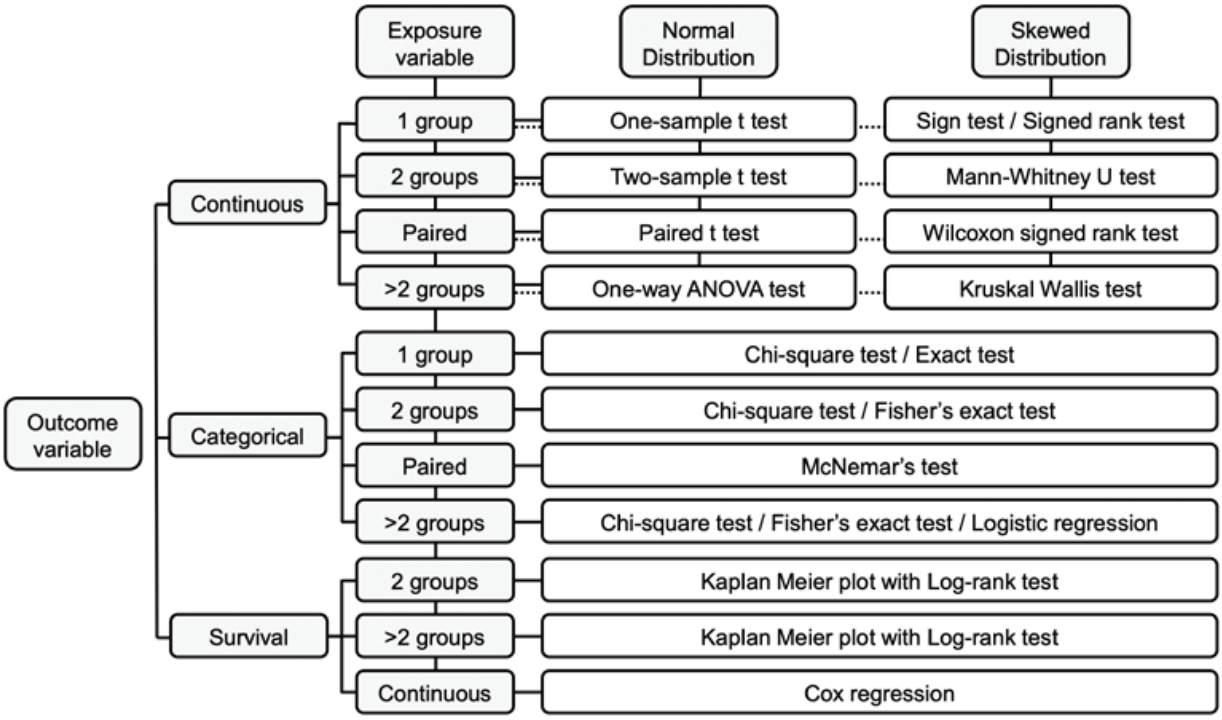

Figure 1. Flowchart of representative statistical tests.

Information from: Baker WE, Sowinski KM. Biostatistics and study designs: fundamentals of design and interpretation. In: Updates in Therapeutics®: Cardiology Pharmacy Preparatory Review Course. ACCP, 2018.

E. Comparing Groups, Continuous and Ordinal Data
   1. Parametric tests
      a. Student t-test: Several different types
         i. One-sample test: Compares the mean of the study sample with the population mean

Group 1	Known population mean

         ii. Two-sample, independent samples, or unpaired test: Compares the means of two independent samples. This is an independent samples test.

Group 1	Group 2

            (a) Equal variance test
               (i) Rule for variances: If the ratio of larger variance to smaller variance is greater than 2, we generally conclude the variances are different.
               (ii) Formal test for differences in variances: *F* test
               (iii) Adjustments to data can be made for cases of unequal variance.
            (b) Unequal variance test: Correction applied
         iii. Paired test: Compares the mean difference of paired or matched samples. This is a related-samples test.

Group 1	
Measurement 1	Measurement 2

      b. Analysis of variance (ANOVA): A more generalized version of the t-test that can apply to more than two groups
         i. One-way ANOVA: Compares the means of three or more groups in a study; also known as a single-factor ANOVA. This is an independent samples test.

Group 1	Group 2	Group 3

         ii. Two-way ANOVA: Additional factor (e.g., age) added

Younger groups	Group 1	Group 2	Group 3
Older groups	Group 1	Group 2	Group 3

         iii. Repeated-measures ANOVA: This is a related-samples test. Related measurements

Group 1		
Related Measurements		
Measurement 1	Measurement 2	Measurement 3

         iv. Several more complex factorial ANOVAs can be used.
         v. Many comparison procedures are used to determine which groups actually differ from each other. Post hoc tests: Tukey HSD (honestly significant difference), Bonferroni, Scheffé, Newman-Keuls

c. Analysis of covariance: Provides a method to explain the influence of a categorical variable (independent variable) on a continuous variable (dependent variable) while statistically controlling for other variables

2. Nonparametric tests
   a. Type of data that may require use: continuous data not normally distributed (skewed data) or ordinal data
   b. Tests for independent samples
      i. Wilcoxon rank sum test, Mann-Whitney *U* test, or Wilcoxon-Mann-Whitney test: Compares two independent samples (related to a two-sample t-test)
      ii. Kruskal-Wallis one-way ANOVA by ranks: Compares three or more independent groups (related to a one-way ANOVA)
   c. Tests for related or paired samples
      i. Sign test and Wilcoxon signed rank test: Compares two matched or paired samples (related to a paired t-test)
      ii. Friedman ANOVA by ranks: Compares three or more matched or paired groups

F. Comparing Groups for Categorical or Nominal Data
   a. Independent samples
      i. Chi-square (χ^2) test: Compares expected and observed proportions between two or more groups
         (a) Test of independence
         (b) Test of goodness of fit
      ii. Fisher exact test: Specialized version of the chi-square test for small groups (cells) containing less than five predicted observations
   b. Paired samples
      i. McNemar test: Used to determine whether there are differences on a dichotomous variable between two related groups. Similar to a paired t-test, for this type of data

IX. CORRELATION AND REGRESSION

A. Introduction: Correlation vs. Regression
   1. Correlation examines the strength of the association between two variables. It does not necessarily assume that one variable is useful in predicting the other.
   2. Regression examines the ability of one or more variables to predict another variable.

B. Pearson Correlation
   1. The strength of the relationship between two variables that are normally distributed, ratio or interval scaled, and linearly related is measured with a correlation coefficient.
   2. Often called the degree of association between the two variables
   3. Does not necessarily imply that one variable is dependent on the other (regression analysis will do that)
   4. Pearson correlation (r) ranges from −1 to +1 and can take any value in between:

−1	0	+1
Perfect negative linear relationship	No linear relationship	Perfect positive linear relationship

   5. Hypothesis testing is performed to determine whether the correlation coefficient is different from zero. This test is highly influenced by sample size.

C. Pearls About Correlation
   1. The closer the magnitude of r to 1 (either + or −), the more highly correlated the two variables. The weaker the relationship between the two variables, the closer r is to 0.
   2. There is no agreed-on or consistent interpretation of the value of the correlation coefficient. It is dependent on the environment of the investigation (laboratory vs. clinical experiment).
   3. Pay more attention to the magnitude of the correlation than to the p-value because it is influenced by sample size.
   4. Crucial to the proper use of correlation analysis is the interpretation of the graphic representation of the two variables. Before using correlation analysis, it is essential to generate a scatterplot of the two variables to visually examine the relationship.

D. Spearman Rank Correlation: Nonparametric test that quantifies the strength of an association between two variables but does not assume a normal distribution of continuous data. Can be used for ordinal data or nonnormally distributed continuous data

E. Regression
   1. A statistical technique related to correlation. There are many different types. For simple linear regression, one continuous outcome (dependent) variable and one continuous independent (causative) variable
   2. Two main purposes of regression: Development of prediction model and accuracy of prediction
   3. Prediction model: Making predictions of the dependent variable from the independent variable; $Y = mx + b$ (dependent variable = slope × independent variable + intercept)
   4. Accuracy of prediction: How well the independent variable predicts the dependent variable. Regression analysis determines the extent of variability in the dependent variable that can be explained by the independent variable.
      a. Coefficient of determination (r^2) measured describing this relationship. Values of r^2 can range from 0 to 1.
      b. An r^2 of 0.80 could be interpreted as saying that 80% of the variation in *Y* is explained by the variation in *X*.
      c. This does not provide a mechanistic understanding of the relationship between *X* and *Y* but rather a description of how clearly such a model (linear or otherwise) describes the relationship between the two variables.
      d. Like the interpretation of r, the interpretation of r^2 is dependent on the scientific arena (e.g., clinical research, basic research, social science research) to which it is applied.
   5. For simple linear regression, two statistical tests can be used.
      a. To test the hypothesis that the *y*-intercept differs from zero
      b. To test the hypothesis that the slope of the line is different from zero
   6. Regression is useful in constructing predictive models. The literature is full of examples of predictions. The process involves developing a formula for a regression line that best fits the observed data.
   7. Like correlation, there are many different types of regression analysis.
      a. Multiple linear regression: One continuous independent variable and two or more continuous dependent variables
      b. Simple logistic regression: One categorical response (dependent) variable and one continuous or categorical explanatory (independent) variable
      c. Multiple logistic regression: One categorical response (dependent) variable and two or more continuous or categorical explanatory (independent) variables
      d. Nonlinear regression: Variables are not linearly related (or cannot be transformed into a linear relationship). This is where our pharmacokinetic equations come from.
      e. Polynomial regression: Any number of response and continuous variables with a curvilinear relationship (e.g., cubed, squared)

8. Example of regression
    a. The following data are taken from a study evaluating enoxaparin use. The authors were interested in predicting patient response (measured as anti-factor Xa concentrations) from the enoxaparin dose in the 75 subjects who were studied.

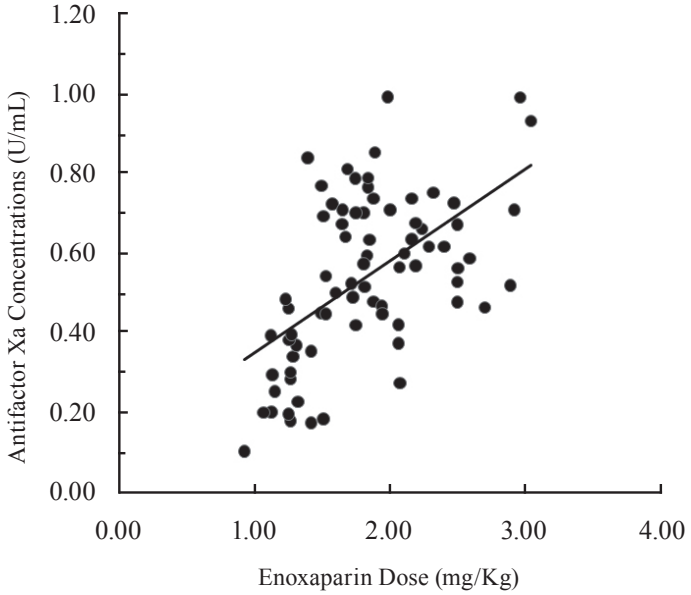

Figure 2. Relationship between antifactor Xa concentrations and enoxaparin dose.

    b. The authors performed regression analysis and reported the following: Slope: 0.227, *y*-intercept: 0.097, $p<0.05$, $r^2 = 0.31$.
    c. Answer the following questions:
        i. What are the assumptions necessary to use regression analysis?
        ii. Provide an interpretation of the coefficient of determination.
        iii. Predict anti-factor Xa concentrations at enoxaparin doses of 2 and 3.75 mg/kg.
        iv. What does the $p<0.05$ value indicate?

X. SURVIVAL ANALYSIS

A. Studies the Time Between Entry in a Study and Some Event (e.g., death, myocardial infarction)
    1. Censoring makes survival methods unique; considers that some subjects leave the study for reasons other than the event (e.g., lost to follow-up, end of study period)
    2. Considers that all subjects do not enter the study at the same time
    3. Standard methods of statistical analysis such as t-tests and linear or logistic regression may not be appropriately applied to survival data because of censoring.

B. Estimating the Survival Function
    1. Kaplan-Meier method
        a. Uses survival times (or censored survival times) to estimate the proportion of people who would survive a given length of time under the same circumstances
        b. Allows the production of a table (life table) and a graph (survival curve)
        c. We can visually evaluate the curves, but we need a test to evaluate them formally.

2. Log-rank test: Compare the survival distributions between two or more groups.
    a. This test precludes an analysis of the effects of several variables or the magnitude of difference between groups or the CI (see the text that follows for the Cox proportional hazards model).
    b. H_0: No difference in survival between the two populations
    c. Log-rank test uses several assumptions.
        i. Random sampling and subjects chosen independently
        ii. Consistent criteria for entry or end point
        iii. Baseline survival rate does not change as time progresses.
        iv. Censored subjects have the same average survival time as uncensored subjects.
3. Cox proportional hazards model
    a. Most popular method to evaluate the impact of covariates; reported graphically like Kaplan-Meier
    b. Investigates several variables at a time
    c. Actual method of construction and calculation is complex.
    d. Compares survival in two or more groups after adjusting for other variables
    e. Allows calculation of a hazard ratio (and CI)
4. Example of survival analysis.

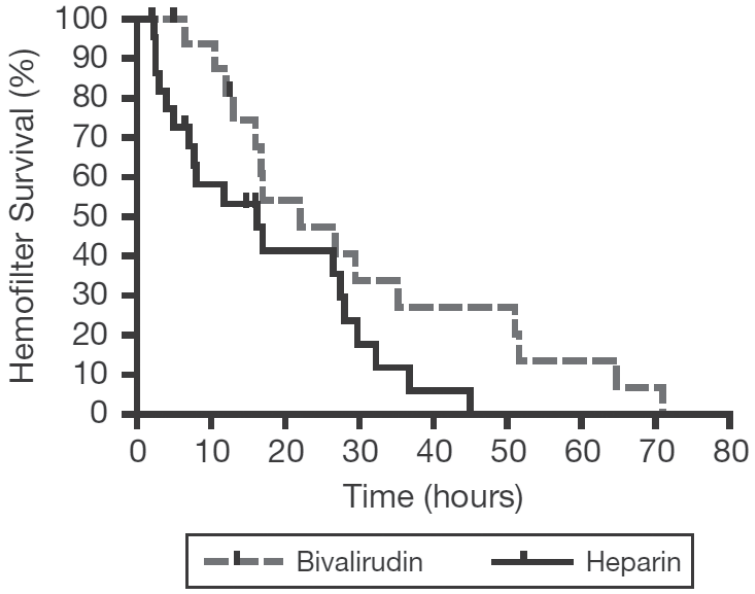

Figure 3. Hemofilter survival with bivalirudin versus heparin in patients receiving continuous renal replacement therapy.

Source: Kiser TH, MacLaren R, Fish DN, et al. Bivalirudin versus unfractionated heparin for prevention of hemofilter occlusion during continuous renal replacement therapy.

Pharmacotherapy 2010;30:1117-26.

XI. SUMMARY OF SELECTING STATISTICAL TESTS

Table 7. Representative Statistical Tests

Type of Data				
Goal	**Continuous Quantitative (from Normal Distribution Population)**	**Ordinal, or Quantitative (from Nonnormal Distribution)**	**Nominal or Named (Two Possible Outcomes)**	**Survival Time**
Descriptive	Mean, SD	Median, interquartile range, range	Proportion or percent	Kaplan Meier curve
Compare one group to a known value	One-sample *t* test	One sample Wilcoxon sign test	Chi-square or binomial test[b]	
Compare two independent groups	Unpaired *t* test (equal or unequal variance)	Wilcoxon rank sum test[a]	Fisher's exact test (for small samples), chi-square	Log-rank test
Compare two paired or related groups	Paired *t* test	Wilcoxon sign-rank test, sign test	McNemar's test	Conditional proportional hazards regression[b]
Compare three or more independent groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox proportional hazard regression
Compare three or more related groups	Repeated-measures ANOVA	Friedman ANOVA test	Cochrane Q	Conditional proportional hazards regression[b]
Quantify association between two variables	Pearson correlation	Spearman rank correlation	Contingency coefficients[b]	
Predict value from another measured variable	Simple linear regression or nonlinear regression[b]	Nonparametric regression[b]	Simple logistic regression[b]	Cox proportional hazard regression
Predict value from several measured or binomial variables	Multiple linear regression[b] or multiple nonlinear regression[b]		Multiple logistic regression[b]	Cox proportional hazard regression

[a]Wilcoxon rank sum test = Mann-Whitney *U* test = Wilcoxon-Mann-Whitney

[b]Not covered in this chapter or presentation

ANOVA = analysis of variance; SD = standard deviation.

Source: Modified from Motulsky H. Intuitive Biostatistics. Oxford Press, 2015; DiCenzo R, ed. Clinical Pharmacist's Guide to Biostatistics and Literature Evaluation. ACCP, 2015.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The NYHA functional class is an ordinal scale from I (no symptoms) to IV (severe symptoms). Neither ANOVA nor ANCOVA is appropriate for ordinal or noncontinuous data (Answers C and D are incorrect); instead Friedman ANOVA (the nonparametric test) is appropriate. The Wilcoxon signed-rank test is an appropriate nonparametric test to use for paired ordinal data, such as the change in NYHA functional class over time on the same person (Answer B is incorrect). The Kruskal-Wallis test is the nonparametric analog of a one-way ANOVA and is appropriate for this analysis (Answer A is correct).

2. Answer: C

You cannot determine which finding is more important (in this case, the best drug) on the basis of the p-value (i.e., a lower p-value does not mean more important) (Answer B is incorrect). All statistically significant results are interpreted as significant without respect to the size of the p-value. This trial had four independent samples, and use of the unpaired (independent samples) t-test is not appropriate because it requires several unnecessary tests and increases the chances of making a type I error (Answer A is incorrect). In this setting, ANOVA is the correct test (Answer C is correct), followed by a multiple-comparisons procedure to determine where the actual differences between groups lie. A paired t-test is inappropriate because this is a parallel-group trial (Answer D is incorrect). Use of ANOVA in this case assumes a normal distribution and equal variance in each of the four groups.

3. Answer: D

The typical a priori α error (type I) rate is 5% (i.e., when the study was designed, the error rate was designed to be 5% or less). The actual type I error rate is reported in the question as 0.01 (1%) (Answer A is incorrect). Answers B and C are related; the study did have enough power because a statistically significant difference was observed. Similarly, a type II error was not made because this error has to do with not finding a difference when one truly exists. In this question, the type I error rate is 1%, the value of the p-value (Answer D is correct).

4. Answer: C

Sample sizes need not be equal to use a t-test (Answer A is incorrect). Body mass index data are not ordinal but continuous; thus, a t-test is appropriate (Answer B is incorrect). The assumption of equal variances is required to use any parametric test (Answer C is correct). A specific value for power is not required to use a test (Answer D is incorrect).

5. Answer: B

The reporting of the mean difference and CI is thought by many to be a superior means of presenting the results from a clinical trial because it describes both precision and statistical significance, as compared with a p-value, which distills everything into one value, making Answer A incorrect. The presentation of the data in this manner clearly shows all the necessary information for making the appropriate conclusion. To assess statistical significance by use of CIs, the 95% CI (corresponding to the 5% type I error rate used in most studies) may not contain zero (signifying no difference between men and women) for the mean difference, making Answer D incorrect. Answer B is correct because the p-value of less than 0.05 corresponds to the 95% CI in that item. To evaluate Answer C, we would need to know the 99% CI.

6. Answer: D

Answer A is incorrect because it uses unconventional approaches to determine statistical significance. Although this can be done, it is unlikely to be accepted by other readers and investigators. This study observed a nonsignificant increase in HDL concentration between the two groups. With a small sample size, such as the one used in this study, there is always concern about adequate power to observe a difference between the two treatments. A difference may exist between these two drugs, but the number of subjects studied may be too small to detect it statistically. Answer D is correct because, with the lack of information provided in this narrative, it is not possible to estimate power; thus, more information is needed. Answer B may be correct, but without first addressing the question of adequate power, it would be an inappropriate conclusion to draw. Answer C is incorrect because even though the new drug increased HDL concentration more than the other treatment, it is inappropriate to conclude that it is better because, statistically, it is not.

7. Answer: B

The primary end point in this study, the percentage of subjects at or below the target blood pressure, is nominal data. Subjects at target blood pressure (less than 140/90 mm Hg) are defined as having reached the target. This type of data requires either a chi-square test or a Fisher's exact test (depending on the sample size or, more accurately, the number of counts in the individual contingency table cells) (Answer B is correct). An independent samples t-test is not appropriate because actual blood pressure values are not being compared (at least not in this question or this end point) (Answer A is incorrect). If we were comparing the actual blood pressure between the two groups, the test might be appropriate if parametric assumptions were met. The Wilcoxon signed-rank test is the appropriate nonparametric test for comparing paired samples (usually in a crossover trial) (Answer C is incorrect). Finally, a one-sample t-test is used to compare the mean of a single group with the mean of a reference group. This is also incorrect in this situation because two groups are being compared (Answer D is incorrect).

8. Answer: A

Detecting the smaller difference between the treatments requires more power. Power can be increased in several different ways. Answer A is correct because the most common approach is to increase the sample size, which is expensive for the researchers. Answer D is incorrect because smaller sample sizes diminish a study's ability to detect differences between groups. Power can also be increased by increasing α, but doing so increases the chances of a type I error. Answer B decreases α, thus making it more difficult to detect differences between groups. Answer C certainly makes it easier to detect a difference between the two groups, but it uses an unconventional α value and is thus not the most appropriate technique.

9. Answer: C

Regression analysis is the most effective way to develop models to predict outcomes or variables (Answer C is correct). There are many different types of regression, but all share the ability to evaluate the impact of multiple variables simultaneously on an outcome variable. Correlation analysis is used to assess the association between two (or more) variables, not to make predictions (Answer A is incorrect). Kaplan-Meier curves are used to graphically depict survival curves or time to an event (Answer B is incorrect). Confidence intervals are not used to make predictions (Answer D is incorrect).

Study Designs: Fundamentals and Interpretation

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Study Designs: Fundamentals and Interpretation

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Learning Objectives

1. Evaluate the concepts and sources of internal and external validity, bias, and confounding in clinical study design.
2. Outline the hierarchy of evidence and advantages and disadvantages of various study designs.
3. Evaluate odds, odds ratio, risk/incidence rate, risk ratio/relative risks (RRs), and other risk estimates.
4. Evaluate the computed number needed to treat.
5. Define point and period prevalence, incidence rate, prevalence rate, absolute risk difference, and RR difference.

Abbreviations in This Chapter

ALA	α-linolenic acid
AR	Absolute risk
ARD	Absolute risk difference
ARR	Absolute risk reduction
CI	Confidence interval
HR	Hazard ratio
MI	Myocardial infarction
NNT	Number needed to treat
OR	Odds ratio
PPA	Phenylpropanolamine
RR	Risk ratio/relative risk
RRD	Relative risk difference
RRR	Relative risk reduction
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of the chapter.

Questions 1 and 2 pertain to the following case.

A recently released statin is associated with less myopathy than other currently available statins. After 2 years of use, a retrospective case-control study was undertaken by the manufacturer after 20 different reports of severe myopathy were sent to the U.S. Food and Drug Administration's (FDA's) MedWatch program. Risk factors for statin-induced myopathy were not assessed; however, both the cases and the controls of this study had identical diagnostic evaluations and were stratified according to the duration of statin use before the onset of myopathy.

1. Which type of bias is this study design most susceptible to?
   A. Confounding by indication.
   B. Recall bias.
   C. Diagnostic bias.
   D. Misclassification.

2. Which factor will be most affected by the type of bias likely to occur in this study?
   A. External validity.
   B. Internal validity.
   C. Assessment of exposure.
   D. Number of patients needed for the study.

3. When describing the results of a randomized controlled clinical trial, the investigators report using an intention-to-treat analysis to analyze their data. The results of their investigation comparing two diuretics for heart failure show no difference in the number of hospitalizations for decompensated heart failure between the treatment groups. Given their method of data analysis, which statement is most appropriate?
   A. May be susceptible to issues regarding recall bias.
   B. Provides a good measure of effectiveness under typical clinical conditions.
   C. Cannot provide an estimate of the method's effectiveness.
   D. May overestimate the actual treatment effect.

4. A prospective randomized study compared once-daily enoxaparin with twice-daily enoxaparin when treating patients with venous thromboembolism (VTE). One of the study end points was the recurrence of VTE. The following table summarizes recurrence rates in all patients.

	Once Daily	Twice Daily
All patients, n (%)	13/298 (4.4)	9/312 (2.9)

   The 95% confidence interval (CI) for the difference in recurrence rates between the two groups was −1.5% to 4.5%. Which conclusion is most appropriate?
   A. Twice-daily enoxaparin is superior to once daily

B. Superiority of twice-daily enoxaparin could not be established over once daily.

C. Once-daily enoxaparin is superior to twice-daily enoxaparin.

D. No conclusion can be drawn because p-values are unavailable.

5. According to the data in the previous question and the result obtained, which best represents the number of patients who would need to be treated (NNT) with twice-daily enoxaparin to prevent the recurrence of one VTE episode?

A. NNT would be 2.

B. NNT would be 67.

C. NNT would be 152.

D. NNT should not be calculated because the result was nonsignificant.

Questions 6 and 7 pertain to the following case.
A multicenter, double-blind, placebo-controlled trial randomly assigned 4837 patients to treatment with margarine supplemented with the omega-3 fatty acid α-linolenic acid (ALA) (margarine with ALA) or a placebo margarine. The primary combined end point was the rate of cardiovascular events, defined as fatal and nonfatal cardiovascular events and percutaneous coronary interventions. Data were analyzed according to intention-to-treat analysis with the use of a Cox proportional hazards model. The hazard ratio (HR) and 95% CI for the margarine with ALA group were 0.91 and 0.78–1.05, respectively. In the prespecified subgroup of women, margarine with ALA was associated with an HR of 0.73 (95% CI, 0.51–1.03).

6. Which statement is most appropriate?

A. Margarine with ALA statistically significantly reduced the risk of cardiovascular events ($p<0.05$).

B. Margarine with ALA statistically significantly reduced the risk of cardiovascular events ($p<0.01$).

C. Margarine with ALA did not significantly reduce the risk of cardiovascular events ($p>0.05$).

D. Without a p-value, it is not possible to determine whether margarine with ALA affected cardiovascular events.

7. When the study was being designed, which choice describes the outcome for which the study was most likely to have been powered?

A. Differences in the rate of cardiovascular events.

B. Differences in the rate of percutaneous coronary interventions.

C. Differences in the rate of the composite outcomes in women.

D. Differences in the rate of the composite outcomes in men.

8. In a meta-analysis of studies examining the effects of several antihypertensive drugs, the odds ratio (OR) for treatment with low-dose diuretics compared with calcium channel blockers for cardiovascular disease events was 0.84 (95% CI, 0.75–0.95). Which statement is the most appropriate interpretation of these findings?

A. Treatment of hypertension with low-dose diuretics was more effective in preventing cardiovascular disease events than treatment with calcium channel blockers.

B. Treatment of hypertension with calcium channel blockers was more effective in preventing cardiovascular disease events than treatment with low doses of diuretics.

C. The difference observed between treatment with calcium channel blockers and low doses of diuretics is not statistically significant.

D. The odds of developing cardiovascular events when treating hypertension with low doses of diuretics are lower than when using calcium channel blockers.

BPS Pharmacotherapy Specialty Examination Content Outline

2. Application of Evidence to Practice and Education
    a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Sub-task(s): 2.1.5
    b. 2.2. Evaluate pharmacotherapy-related literature and health information. Sub-task(s): 2.2.1, 2.2.2, 2.2.5 - 2.2.13

I. INTRODUCTION: WHY DO PHARMACISTS NEED TO KNOW ABOUT STUDY DESIGN AND INTERPRETATION?

A. Pharmacotherapy Specialty Examination content outline, Domain 2: Application of Evidence to Practice and Education (25%)

B. Subgroups:
   1. Retrieve relevant information that addresses pharmacotherapy-related inquiries.
   2. Evaluate pharmacotherapy-related literature and health information.
   3. Disseminate pharmacotherapy-related information to educate health care professionals, patients, and caregivers.

II. VARIOUS CONCEPTS IN STUDY DESIGN

A. Research Design Classification
   1. Study purpose: Descriptive versus analytical
   2. Time orientation: Prospective versus retrospective design
      a. Prospective: Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future.
      b. Retrospective: Begin and end in the present; however, this design involves a major backward look to collect information about events that occurred in the past.
   3. Investigator orientation:
      a. Experimental trials
      b. Quasi-experimental trials
      c. Observational trials

B. Relative Strength of Evidence: Hierarchy of Study Designs: This hierarchy holds assuming that all of the study designs are performed using the best possible techniques (e.g., a poorly conducted RCT is not necessarily higher on the hierarchy than a well-done cohort study)

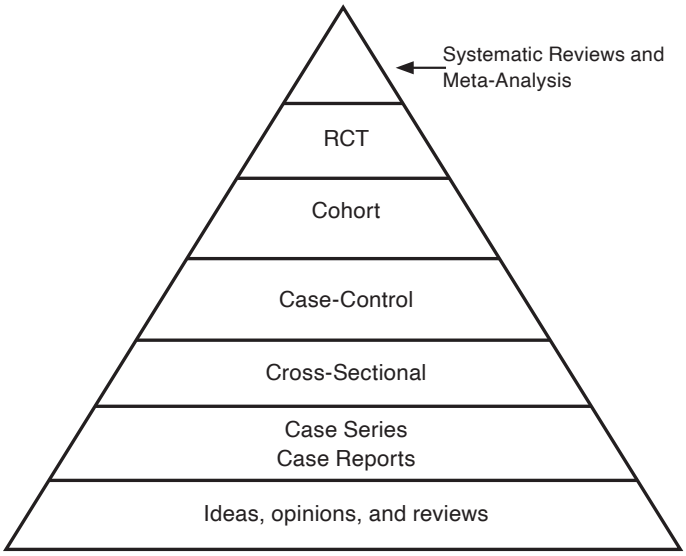

Figure 1. Hierarchy of clinical study design.
RCT = randomized controlled clinical trial.

C. Validity in Study Design
   1. Internal validity
      a. The degree to which the outcome (either efficacy or safety) can be explained by differences in assigned groups
      b. Often related to the study methods; proper design, conduction, and analysis of the study in order to minimize systematic bias
      c. Factors that may affect internal validity:
         i. Poor study design
         ii. Inadequate randomization or allocation of subjects
         iii. Lack of or inappropriate blinding of participants, personnel, and outcome assessors
         iv. Use of imprecise or inaccurate measurements or inappropriate statistical methods
         v. Incomplete outcome data or selective outcome reporting
      d. Limitations are magnified with use of nonrandomized/observational study designs
   2. External validity
      a. The degree to which the findings can be generalized or extrapolated to a population beyond a study
      b. Lack of consideration for external validity is a common criticism of clinical research (regardless of the design) and may explain the underuse of clinical trial results in routine clinical practice
      c. Factors that may affect external validity:
         i. Setting of the trial (health care system, country, selection of participating centers/clinicians)
         ii. Selection of patients (eligibility and exclusion criteria, placebo/treatment run-in period)
         iii. Study patient characteristics (baseline clinical characteristics, racial/ethnic/sex group breakdowns, uniformity of underlying pathology, comorbidities, severity of disease)
         iv. Differences between trial protocol and routine practice (intervention timing, appropriateness of control, background therapy and standardization, frequency of monitoring)
         v. Outcome measures and follow-up (relevance and acceptance of surrogate outcomes, reproducibility of findings, use of patient-centered outcomes, frequency/adequacy of follow-up)
         vi. Adverse effects of treatment (impact of run-in period, discontinuation rates, completeness of adverse drug event reporting, intensity of safety procedures)
      d. Limitations could be minimized with use of pragmatic design (although internal validity is reduced).

D. Random Error in Study Design: A difference between the observed and expected results of a study that is caused by chance, or a nonsystematic error. These errors impact the reliability of the results and can be controlled, but not eliminated. This error diminishes as the study sample gets larger.

E. Bias in Study Design
   1. Definition: A difference between the observed and expected results of a study that is caused by systematic, nonrandom error. Bias can be caused by variation in study methodology and conductance, ultimately introducing error in outcome interpretation. Bias can be broadly categorized as selection bias, measurement bias, and confounding. The most important design techniques used to reduce bias while designing a study are blinding and randomization.
   2. Bias can be controlled or accounted for with appropriate planning in the design, collection, and analysis of data. Bias may have a different impact depending on how the collection data are interpreted.
   3. Examples of bias
      a. Selection bias: An error in the selection or sampling of individuals for a clinical study. This systematic selection leads to an advantage for one group over the other. Selection bias may impact case-control studies more than cohort studies.
      b. Observational or information bias: Incorrect determination of outcomes or exposures. Examples include: An error in the recording of individual factors of a study, such as inaccurate recording of a patient's risk factor or inaccurate recording of the timing of a blood sample

c. Recall bias: Systematic error caused by differences in the accuracy or completeness of the recollections of study participants regarding past events or experiences. For example, cases are more likely to remember exposures than controls.
d. Interviewer bias: Interviews are not conducted in a uniform manner for all study participants
e. Misclassification bias: Subject is categorized into an incorrect group or category potentially altering the association or research outcome.
    i. Differential bias: Bias that occurs when information errors differ between groups being studied (e.g., in a cohort study, between those with the disease and those without). This is a nonrandom error.
    ii. Non-differential bias: Bias that occurs when the results collected are incorrect but affect both groups the same. This is a systematic error.
f. Publication bias: Studies that report positive findings are more likely to be published than studies that report negative findings.

F. Confounding in Study Design
1. A nonrandomized variable that affects the independent or dependent variable, altering the ability to determine the true effect on the measured outcome. These factors may hide or exaggerate a true association.
2. To minimize the potential for missing a confounding variable, all relevant information should be collected and evaluated. During the design, subjects should be randomized or matched in the analysis by stratification, by propensity score matching, or by use of multivariable analysis techniques.

G. Factors Important in Assessing Causality:
1. Temporality: Cause before effect
2. Strength: Plausibility increases with strength of relationship
3. Biological gradient: Dose-response
4. Consistency: Observations over several settings
5. Specificity: Single cause for effect
6. Plausibility: Biologically
7. Coherence: Consistency with existing knowledge
8. Analogy: Preclinical expectation applied to clinical testing
9. Experimental design

III. CASE REPORTS/CASE SERIES

A. Document and Describe Experiences, Novel Treatments, and Unusual Events. Allows hypothesis generation that can be tested with other study designs. Note that the title does not state "study."
1. Possible adverse drug reactions in one or more patients
    a. QT-interval prolongation associated with fluoroquinolone antibiotics
2. Case report: One patient
3. Case series: More than one patient with a similar experience or many case reports combined into a descriptive review
4. Reports should provide sufficient detail to allow readers to recognize same/similar cases at their center/practice.
5. The Case Report (CARE) guidelines describe what information should be included in a case report.

B. Advantages and Disadvantages
   1. Advantages: Hypotheses are formed, which may be the first step in describing an important clinical problem. Easy to perform and inexpensive
   2. Disadvantages: Does not provide explanation other than conjecture and does not establish causality or association

IV. OBSERVATIONAL STUDY DESIGNS

A. Design Does Not Involve Investigator Intervention, Only Observation. It is essential to remember that observational study designs investigate associations—cannot prove causation.

B. Case-Control Study: Study Exposure in Those with and without the Outcome of Interest

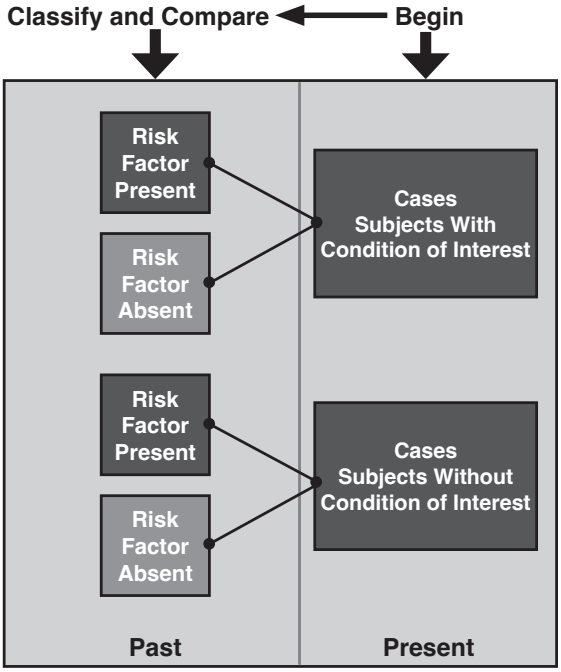

Figure 2. Case-control study design.

   1. Determine the association between exposures/risk factors and disease/condition. Classic example: Aspirin use and Reye syndrome
   2. Retrospective studies
   3. Practical method to study exposures in rare diseases or diseases that take long periods to develop
   4. Critical assumptions to minimize bias
      a. Cases are selected to be representative of those who have the disease. Randomly select cases when possible.
      b. Controls are representative of the general population that does not have the disease and are as identical as possible to the cases, minus the presence of the disease.
      c. Information is collected from cases and controls in the same way.

5. Examples
    a. Risk of myocardial infarction associated with antihypertensive drug therapies (JAMA 1995;274: 620-5)
        i. Purpose of the study: To estimate the association between myocardial infarction (MI) and use of antihypertensives
        ii. Disease: Myocardial infarction. Exposure: Antihypertensives
        iii. Cases (n=623): Hypertensive patients who sustained a first fatal or nonfatal MI. Controls (n=2032): Patients with hypertension matched for age, sex, and calendar year. All 623 cases and 2032 controls had pharmacologically treated hypertension.
        iv. Data collection: Review of medical record; telephone interview of consenting survivors. Exposure (antihypertensive therapy) was assessed using the computerized pharmacy database.
    b. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke (N Engl J Med 2000;343:1826-32). Purpose of study:
        i. To estimate in women the association between hemorrhagic stroke and the use of appetite suppressants containing PPA
        ii. To estimate the association between any use of PPA (in appetite suppressant or cough or cold remedy) and hemorrhagic stroke
        iii. To estimate in men and women the association between hemorrhagic stroke and the type of exposure to PPA
        iv. Disease: Hemorrhagic stroke (several types). Exposure: PPA
        v. Cases: Symptomatic subarachnoid or intracerebral hemorrhage (n=702). Controls: Matched by sex, race, and age (n=1376)
        vi. Exposure assessed by structured questionnaire, product photographs, and ingredient confirmation
6. Advantages
    a. Inexpensive and can be conducted quickly
    b. Allows investigation of several possible exposures or associations, particularly when risk factors are unknown.
7. Disadvantages
    a. Confounding must be controlled.
    b. Observational and recall bias: Looking back to recall exposures and their possible levels of exposure
    c. Selection bias: Case selection and control matching are difficult.
8. Measure of association: OR (odds ratio): The OR is interpreted as the odds of exposure to a factor in those with a condition or disease compared with those who do not have the condition or disease. Interpretation of these concepts will be presented below.

C. Cohort Study
1. Determines the association between exposures/factors and disease/condition development. Allows an estimation of the risk of outcome (and the RR between the exposure groups). Study outcome of interest in those with and without the exposure of interest. Classic examples follow:
    a. Framingham Study. A prospective "cohort" of subjects from Framingham, Massachusetts, were (and are) studied over time to evaluate the relationship between a variety of conditions (exposures) on the development of cardiovascular disease (summarized in Int J Epidemiol 2015;44:1800-13).
    b. Nurses' Health Study: Prospective study that investigated the potential long-term consequences of the use of oral contraceptives (summarized in BMJ 2014;349:g6356)
    c. Thimerosal DTP (diphtheria-tetanus-whole-cell pertussis) vaccine study: Retrospective cohort study that investigated the impact of thimerosal on developmental neurologic disorders (Pediatrics 2004;114:584-91)

2. Describes the incidence or natural history of a disease/condition and measures it in time sequence
3. Retrospective (historical): Begins and ends in the present but involves a major backward look to collect information about events that occurred in the past

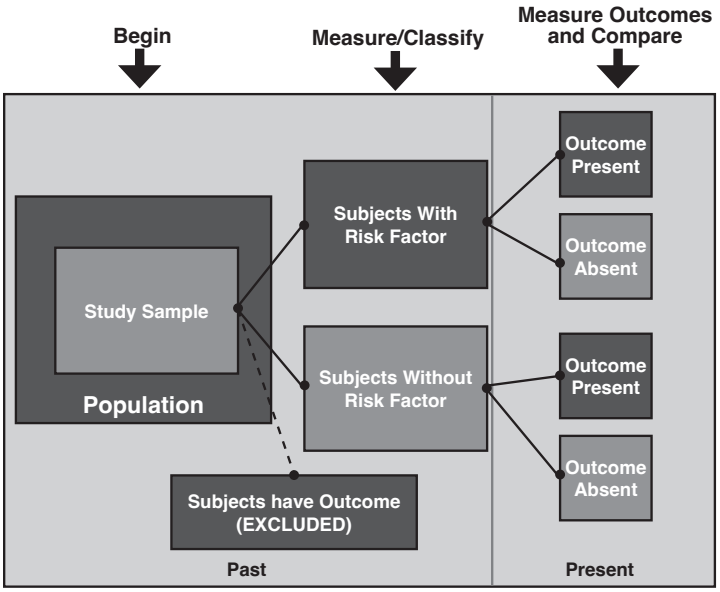

Figure 3. "Retrospective" (historical) cohort study design.

   a. Advantages: Less expensive and time-consuming; no loss to follow-up, ability to investigate issues not amenable to a clinical trial or ethical or safety issues
   b. Disadvantages: Only as good as the data available, little control of confounding variables through nonstatistical approaches, recall bias
4. Prospective or longitudinal: Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future

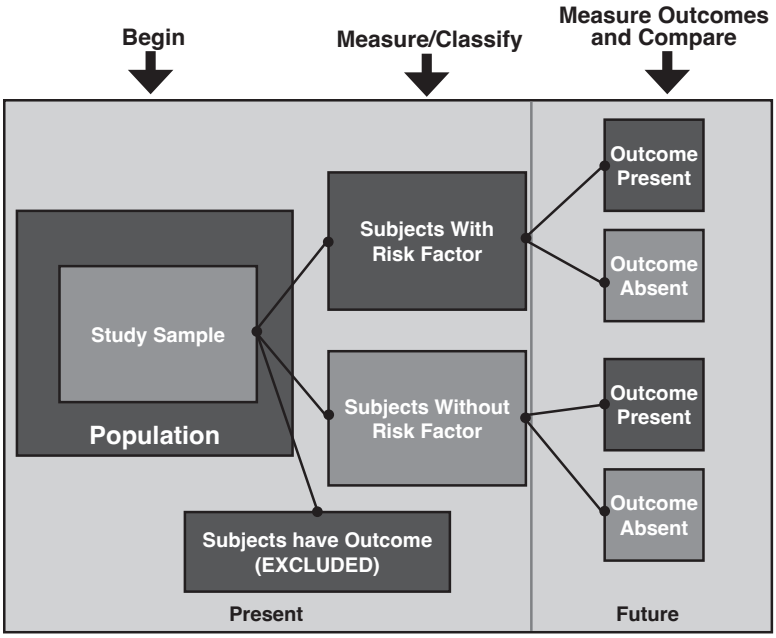

Figure 4. Prospective cohort study design.

a. Example: Prospective, observational study: Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study (Ann Intern Med 2001;135:1-8)
b. Advantages: Can control for confounding factors to a greater extent, easier to plan for data collection
c. Disadvantages: More expensive and time-intensive, loss of subject follow-up, difficult to study rare diseases/conditions at a reasonable cost

5. Measure of association: RR: The risk of an event or development of a condition relative to exposure; the risk of someone developing a condition when exposed compared with someone who has not been exposed

D. Cross-sectional (a.k.a. prevalence study)
1. Identify the prevalence or characteristics of a condition in a group of individuals.
2. Examples
a. Population-based, cross-sectional study: Prevalence of serious eye disease and visual impairment in a north London population (BMJ 1998;316:1643-7)
b. Cross-sectional analysis of data from a large cohort study: Maternal characteristics and migraine pharmacotherapy during pregnancy (Cephalgia 2009;29:1267-76)
3. Advantages: Easy design, "snapshot in time," all data collected at one time, studies are accomplished by questionnaire, interview, or other available biomedical information (e.g., laboratory values)
4. Disadvantages: Does not allow the study of a factor (or factors) in individual subjects over time, just at the time of assessment; difficult to study rare conditions

V. INCIDENCE, PREVALENCE, RELATIVE RISK/RISK RATIOS, ODDS RATIOS, AND HAZARD RATIOS

A. Incidence
1. Measure of the probability of developing an event or condition
2. Incidence rate: Number of new cases of an event or condition per population in a specified time
3. Calculated by dividing the number of individuals who develop an event or condition during a given period by the number of individuals who were at risk of developing an event or condition during the same period

B. Prevalence
1. Measure of the number of individuals who have an event or condition at any given time
2. Point prevalence: Prevalence on a given date
3. Period prevalence: Prevalence in a period (e.g., year, month)

C. Interpreting Risk Ratios (RR, OR, HR)
1. Estimate the magnitude of association between exposure and an event or condition. Key point: For observational studies, this is not cause and effect; it is an association.
2. The RR and OR differ in how they are interpreted and calculated.
a. The RR is the incidence of an event in the exposed group divided by the incidence of the event in the unexposed (control) group.
b. The OR is the odds of an event occurring in the exposed group divided by the odds of the event occurring in the control group.
3. The RR cannot be directly calculated for most case-control studies because the baseline risk is not available; instead, the OR is the risk ratio utilized. The RR can, however, be calculated for prospective studies, including cohort studies, because the baseline risk can be estimated.

4. The HR differs from the OR and RR in that it can estimate risk at any given point of time within a time period, whereas OR and RR are estimates of the risk over a period of time.
5. When interpreting ratios, the point of unity (no difference) is 1. The RR, OR, and HR are, therefore, interpreted based on their difference from unity (see Table 1). If the 95% confidence interval includes 1, then there is no statistical difference between groups.
6. Interpretation of the index of risk, including RR, OR, and HR
   a. Direction of risk

Table 1. Direction of Risk Associated with OR, RR and HR

RR/OR/HR	Interpretation
< 1	Negative association RR: Risk of disease is lower in the exposed group OR: Odds of exposure/having an outcome is lower in the diseased group HR: Event rates are lower in the experimental group than control group (experimental treatment is better than control treatment)
= 1	No association RR: Risk of disease in the two groups is the same OR: Odds of exposure/having an outcome in the two groups is the same HR: Event rates are the same in both groups
> 1	Positive association RR: Risk of disease is greater in the exposed group OR: Odds of exposure/having an outcome is greater in the diseased group HR: Event rates are higher in the experimental group than control group (experimental treatment is worse than control treatment)

HR = hazard ratio; OR = odds ratio; RR = relative risk/risk ratio.

   b. Magnitude of risk

Table 2. Magnitude of Risk Associated with OR and RR

RR/OR	Interpretation
0.75	RR: 25% reduction in the risk OR: Odds are 0.75/1
1.0	No difference in risk/odds
1.5	RR: 50% increase in the risk OR: Odds are 1.5/1 higher
3.0	RR: 200% (3-fold increase in the risk) OR: Odds are 3/1 higher

7. Calculating RR/OR/contingency tables

Table 3. Contingency Table for Estimating RR and OR

		Event or Condition?	
		Yes	No
Exposure?	Yes	A	B
	No	C	D

a. $RR = \frac{A/(A+B)}{C/(C+D)}$

b. $OR = \frac{\frac{A}{C}}{\frac{B}{D}}$ or = (A x D)/(B x C)

8. Example (PPA study): N Engl J Med 2000;343:1826-32

Table 4. Contingency Table

		Event? Hemorrhagic Stroke in Women	
		Yes	No
Exposure? Appetite suppression use	Yes	6	1
	No	377	749

From: Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.

a. OR = (6/377)/(1/749) = 12
b. Data from the PPA study above related to appetite suppressant and development of hemorrhagic stroke

Table 5. Use of PPA and Appetite Suppressants and the Risk of Developing Hemorrhagic Stroke

	Cases (+ hemorrhagic stroke) n=383	**Controls** (− hemorrhagic stroke) n=750	**Adjusted OR** (95% CI)
Appetite suppressant: Women	6	1	16.6 (1.51–182)
Appetite suppressant: Men	0	0	—
Appetite suppressant: Either	6	1	15.9 (1.38–184)
PPA: Women	21	20	1.98 (1.00–3.90)
PPA: Men	6	13	0.62 (0.20–1.92)
PPA: Either	27	33	1.49 (0.84–2.64)

CI = confidence interval; OR = odds ratio; PPA = phenylpropanolamine.

c. What do these numbers mean?
d. Can you interpret the point estimate and 95% CI in all cases?
   i. What does the point estimate mean?
   ii. What does the CI mean?
   iii. Which ones are statistically significant?

D. Causation
1. REMEMBER: We do not prove or show causality with observational studies, but there is some general "guidance" to consider when evaluating them. It is important to recognize that, in certain situations, the conduct of studies to establish causality is not possible, practical, or ethical (e.g., exposure to a drug leading to a birth defect or exposure to an environmental factor leading to the development of cancer).

2. Questions used to evaluate causality
    a. Was statistical significance observed?
    b. What was the strength of the association, as measured by the OR, RR, or HR?
    c. Were dose-response relationships evaluated?
    d. Was there a temporal relationship between exposure and disease/outcome?
    e. Have the results been consistently shown?
    f. Is there biologic plausibility to the association?
    g. Is there any experimental (e.g., animal, in vitro) evidence?

VI. RANDOMIZED CONTROLLED TRIAL DESIGN

A. Characteristics
1. Experimental or interventional, investigator makes intervention and evaluates cause and effect. Examine etiology, cause, efficacy, using comparative groups.
2. Some previous background information or studies should exist to suggest that the intervention used will likely be beneficial.
3. Design allows assessment of causality.
    a. Sufficient cause
    b. Necessary cause
    c. Risk factor
4. Minimizes bias through randomization and/or stratification
    a. Randomization
    b. Block randomization
    c. Stratification
    d. Cluster randomization
5. Treatment controls
    a. Placebo controlled
    b. Active controlled
    c. Historical control
6. Blinding methods
    a. Single-blind: Either subjects or investigators are unaware of subject assignment to active/control.
    b. Double-blind: Both subjects and investigators are unaware of subject assignment to active/control.
    c. Triple-blind: Both subjects and investigators are unaware of subject assignment to active/control; in addition, an analysis group is unaware.
    d. Double-dummy: Method used to match active and control therapies when there are differences in delivery.
        i. Example: One group receives treatment twice-a-day and the other receives treatment once-a-day. The once-a-day group will receive a placebo for the second dose.
        ii. Example: One group receives an oral medication and the other group receives an intravenous medication. The oral group will receive an intravenous placebo and the intravenous group will receive an oral placebo.
    e. Open-label (Nonblind): Everyone is aware of subject assignment to active/control.
7. May use parallel or crossover design (see additional information below)
    a. Crossover provides practical and statistical efficiency to the same degree as a parallel design.
    b. Crossover is not appropriate for certain types of treatment questions (e.g., effect of treatment on a disease that worsens quickly over time or worsens during the study period).
8. Factorial design: Designed to answer two separate research questions in a single group of subjects

9. Examples
    a. Clinical trial: Comparison of two drugs, comparison of two behavioral modifications, etc.
    b. Educational intervention: Online course versus lecture class format
    c. Health care intervention: Pharmacist-based health care team versus non–pharmacist-based health care team

B. Randomized Controlled Trial: Parallel Design

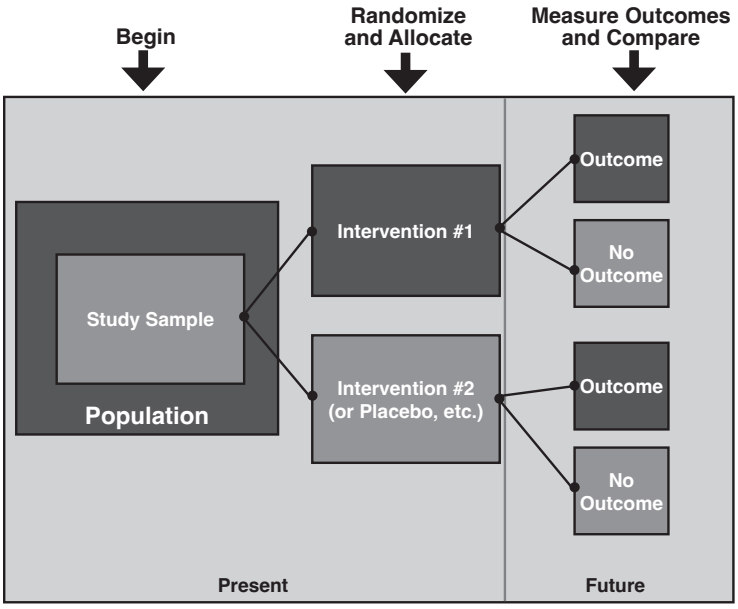

Figure 5. Randomized controlled trial: parallel design.

C. Randomized Controlled Trial: Crossover Design

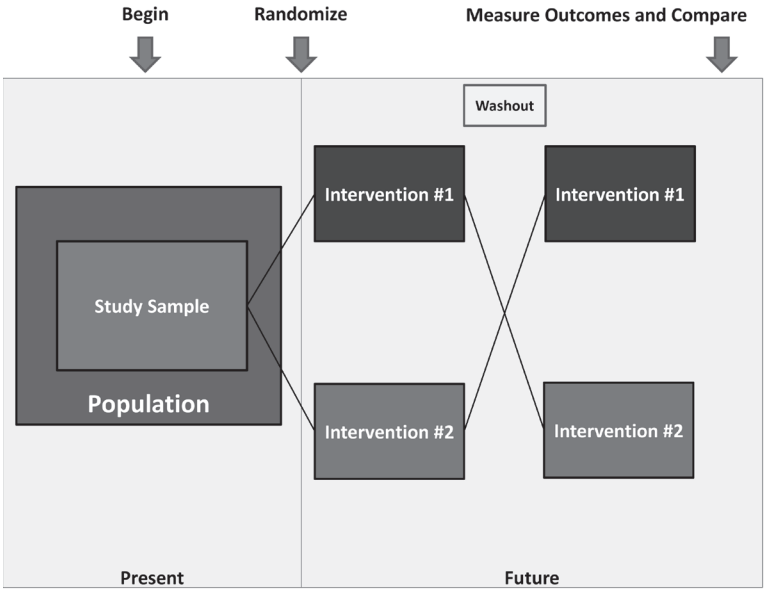

Figure 6. Randomized controlled trial: crossover design.

D. RCT: Factorial Design

E. Examples of Considerations for Controlled Trials
   1. Are the results of the study valid (methods)?
      a. Did the subjects undergo randomization, and what was the randomization technique? Did the randomization process result in equal baseline characteristics?
      b. Were all subjects who entered the trial accounted for? Was follow-up complete? If not, how many were lost to follow-up, from which groups did they leave, and why?
      c. Were subjects analyzed in the groups to which they were randomized? Was intention-to-treat, per-protocol, or actual treatment analysis used?
      d. How was blinding conducted (e.g., subject, investigator), if applicable?
      e. Were the inclusion and exclusion criteria appropriate, or were they too restrictive or inclusive? Were the groups similar at the start of the trial?
      f. Was the sample size sufficient, and was a power calculation included?
      g. Were the groups handled the same way, aside from the intervention(s)?
      h. Were the statistical tests appropriate and understandable?
      i. What was assessed: Surrogate markers or true outcomes? Were *a priori* subgroup analyses performed?
   2. What were the results?
      a. How large was the treatment effect?
      b. How precise was the effect (e.g., based on CIs significant)?
      c. Did the authors properly interpret the results?
   3. Can I apply the results of this study to my patient population? Will they help me care for my patients?
      a. Can the results of this study be applied to general practice?
      b. Was a representative population studied? Can I apply this to my setting?
      c. Do the patients I care for fulfill the enrollment criteria for this study?
      d. Do the patients I care for fulfill the subgroup criteria evaluated?
      e. Do the expected benefits outweigh the expected and/or unanticipated risks?

VII. OTHER ISSUES TO CONSIDER IN CONTROLLED TRIALS

A. Subgroup Analysis
   1. Important part of controlled clinical trials (if set *a priori*)
   2. Many times, they are overused and overinterpreted, leading to unnecessary research, misinterpretation of results, and/or suboptimal patient care.
   3. Many potential pitfalls in identifying and interpreting
      a. Failure to consider several comparisons or to adjust p-values
      b. Problems with sample size (power), classification, and lack of assessment of interaction

B. Composite End Points: Often, the impression is that this practice is not a good practice.
   1. The primary end point is one of the most important decisions to make in the design of a clinical study.
   2. A composite end point combines several end points.
      a. For example, in cardiovascular trials, major adverse cardiovascular events are commonly used and include: Cardiovascular death, nonfatal MI, and nonfatal stroke and may also include target vessel revascularization or hospitalization
      b. Usually combines measures of morbidity and mortality
      c. What does the following statement mean? Our findings show that ramipril reduces the rates of death, MI, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients. Treating 1000 patients with ramipril for 4 years prevents about 150 events in around 70 patients.

i. Was there a reduction in all the end points or just in some?
ii. Are all the outcomes just as likely to occur?
iii. Why would the investigators of this trial have been interested in all of these outcomes?

3. What are the benefits of using composite end points?
   a. No single primary outcome
   b. Alleviate problems of multiple testing
   c. Increase number of events, which decreases sample size and cost to the investigator
4. What are the limitations?
   a. Difficulties in interpreting composite end points; consider our earlier example
   b. Misattribution of statistically beneficial effects of composite measure to each of its component end points
   c. Dilution of effects, negative results for relatively common component of composite end point "hide" real differences in other end points. Undue influence exerted on composite end point by "softer" component end points
   d. "Averaging" of overall effect: Problems when component end points move in opposite directions; a sign the composite end point should be abandoned without valid conclusions being drawn
   e. Should all end points be weighed the same, or should death "weigh" more?
5. The results for each individual end point should be reported together with the results for the composite.

C. Surrogate End Points
1. Parameters thought to be associated with clinical outcomes
   a. Blood pressure for stroke prevention
   b. LDL-C reduction for cardiovascular death reduction
      i. Statins: Yes
      ii. Hormone replacement therapy: No
   c. Premature ventricular contraction suppression and reduced mortality
2. Surrogate outcomes do not always predict clinical outcomes.
3. Short-duration studies that evaluate surrogate end points may not be large enough to detect uncommon adverse events.

D. Superiority Versus Equivalence Versus Noninferiority
1. A superiority trial is designed to detect a difference between experimental treatments. This is the typical design in a clinical trial.
2. An equivalence trial is designed to confirm the absence of a meaningful difference(s) between treatments, neither better nor worse (both directions). The key is the definition of the specified margin. What difference is important? One example is a bioequivalence trial.
3. A noninferiority trial is designed to investigate whether a treatment is not clinically worse (not less effective than stated margin, [noninferiority margin] or inferior) than an existing treatment.
   a. It may be the most effective, or it may have a similar effect
   b. Useful when placebo administration is not possible for ethical reasons
   c. ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial): N Engl J Med 2008;358:1547-59.
      i. Designed to evaluate telmisartan, ramipril, or their combination in patients with a high risk of vascular disease
      ii. Objective was to determine whether telmisartan was noninferior to ramipril in the incidence of cardiovascular deaths
      iii. Noninferior margin was defined as 13% or less
   d. Essentials of noninferiority design
      i. Control group must be effective

ii. Current study similar to previous study with control and with equal doses, clinical conditions, and design used
iii. Adequate power is essential, and usually, larger sample sizes are required.
iv. Need to have a clinically defined noninferiority margin a priori
v. May perform both an intention-to-treat and a per-protocol analysis

E. Explanatory vs. Pragmatic Clinical Trials (N Engl J Med 2016;375:454-63)
1. Explanatory trials: Test a physiologic or clinical hypothesis
2. Pragmatic trials: Inform a clinical or policy decision using real-world populations
a. Designed to show the real-world effectiveness of interventions in broad patient populations outside the rigors of a traditional RCT
b. Study participants should be similar to those who would receive the intervention if it were to become standard of care.
c. Investigators involved with routine clinical practice are preferred to experienced trialists, particularly those who work in a group practice setting.
d. Interventions are commonly not masked.
e. End points focus on those that are important to patients (e.g., hospitalizations, quality of life, symptoms) or that have been underrepresented in RCTs.
f. Disadvantage: Generally have lower internal validity

VIII. CONTROLLED CLINICAL TRIALS: ANALYSIS

A. Questions to Consider in Evaluating and Interpreting a Clinical Trial
1. Study design
a. Was the studied sample representative of the population or the individual to whom the results were being applied?
b. Were the inclusion/exclusion criteria appropriate, or were they overly restrictive or inclusive?
c. Sufficient sample size, power, and so forth? Was a power analysis included?
d. Was a study objective and/or hypothesis provided?
e. Was the study blinded and to whom? (subject, investigator, study personnel, or all?)
f. Was a run-in phase used? If so, why? Did it affect the interpretation of the trial?
g. What type of randomization method was performed? Did the randomization process produce equal baseline characteristics between all groups?
2. Outcomes/assessments
a. Were the primary and/or secondary outcomes identified, were they reasonable, and did they apply to clinical practice?
b. Was a composite outcome used, and were all the individual components identified and clearly stated in the methods and results?
c. Were surrogate markers used instead of (or in addition to) clinically relevant outcomes?
3. Analysis
a. What analysis technique was used: Intention-to-treat, as-treated, or per-protocol?
b. Were the statistical tests appropriate?
4. Interpretation: Was the author's interpretation appropriate and within the confines of the study design?
5. Extrapolation
a. Are you applying the results to similar patients in a similar setting?
b. Are there possible additional adverse effects that were not measured in this study?

IX. COMMON APPROACHES TO ANALYZING CLINICAL TRIALS

A. Intention-to-Treat Analysis
   1. Compares outcomes on the basis of initial group assignment or "as randomized." The allocation to groups was how they were "intended to be treated," even though they may not have taken the medication for the duration of the study, dropped out, and did not comply with the protocol.
   2. Determines effect of treatment under usual conditions of use. Analogous to routine clinical practice in which a patient receives a prescription but may not adhere to the prescribed drug regimen.
   3. Gives a conservative estimate of differences in treatments; may underestimate treatment benefits
   4. Most common approach to assessing clinical trial results
   5. This is the preferred type of analysis in a superiority trial.

B. Per-Protocol Analysis
   1. Subjects who do not adhere to allocated treatment are not included in the final analysis; only those who completed the trial and adhered to the protocol (based on some predetermined definition [e.g., 80% adherence])
   2. Provides additional information about treatment efficacy and provides more generous estimates of differences between treatments
   3. Subject to several issues because of factors such as lower sample size and definitions of adherence. Results are more difficult to interpret and would be validly applied only to adherent patients like those in the trial; not necessarily generalizable to all patients
   4. Preferred type of analysis in noninferiority trials, although intention-to-treat analysis is often also used

C. As-Treated Analysis
   1. Subjects are analyzed by the actual intervention received. If subjects were in the active treatment group but did not take active treatment, the data would be analyzed as if they were in the placebo group.
   2. This analysis essentially ignores/destroys the randomization process for those who did not adhere to study design. Results should be interpreted with caution.

X. REVIEWS

A. Narrative Review (nonsystematic review)
   1. Summarizes results of several studies without systematic methods. The review is qualitative and subjective in nature.
   2. These methods would be typical of a standard literature review.

B. Qualitative Systematic Review
   1. Summary that uses explicit methods to perform a comprehensive literature search, critically appraise it, and synthesize the world literature on a specific topic. This is a summary that uses systematic methods to objectively review a topic, but in a qualitative way.
   2. Differs from a standard literature review: The study results are more comprehensively synthesized and reviewed. Studies included in the review are based on specific inclusion/exclusion criteria, so not all students on a given clinical question are included.
   3. As with a controlled clinical trial (or other studies), the key is a well-documented and well-described systematic review.

C. Quantitative Systematic Review (meta-analysis)
   1. Dramatic increase in the number of these types of papers
   2. First meta-analysis probably published in 1904: Assessment of typhoid vaccine effectiveness

3. Systematic review that uses mathematical/statistical techniques to summarize the results of the evaluated studies
4. These techniques may improve on the following:
   a. Calculation of effect size
   b. Increase in statistical power
   c. Interpretation of disparate results
   d. Reduction in bias
   e. Answers to questions that may not be addressable with individual studies
5. Reliant on criteria for inclusion of previous studies and statistical methods to ensure validity. Details of included studies are essential.
6. Elements of trial methodology
   a. Research question
   b. Identification of available studies
   c. Criteria for trial inclusion/exclusion
   d. Data collection and presentation of findings
   e. Calculation of summary estimate: Ideally with forest plot (Figure 7)
   f. Assessment of heterogeneity
      i. Statistical heterogeneity
      ii. Chi^2, Cochran Q, and I^2 are common tests for heterogeneity.
   g. Assessment of publication bias: Funnel plot
   h. Sensitivity analysis

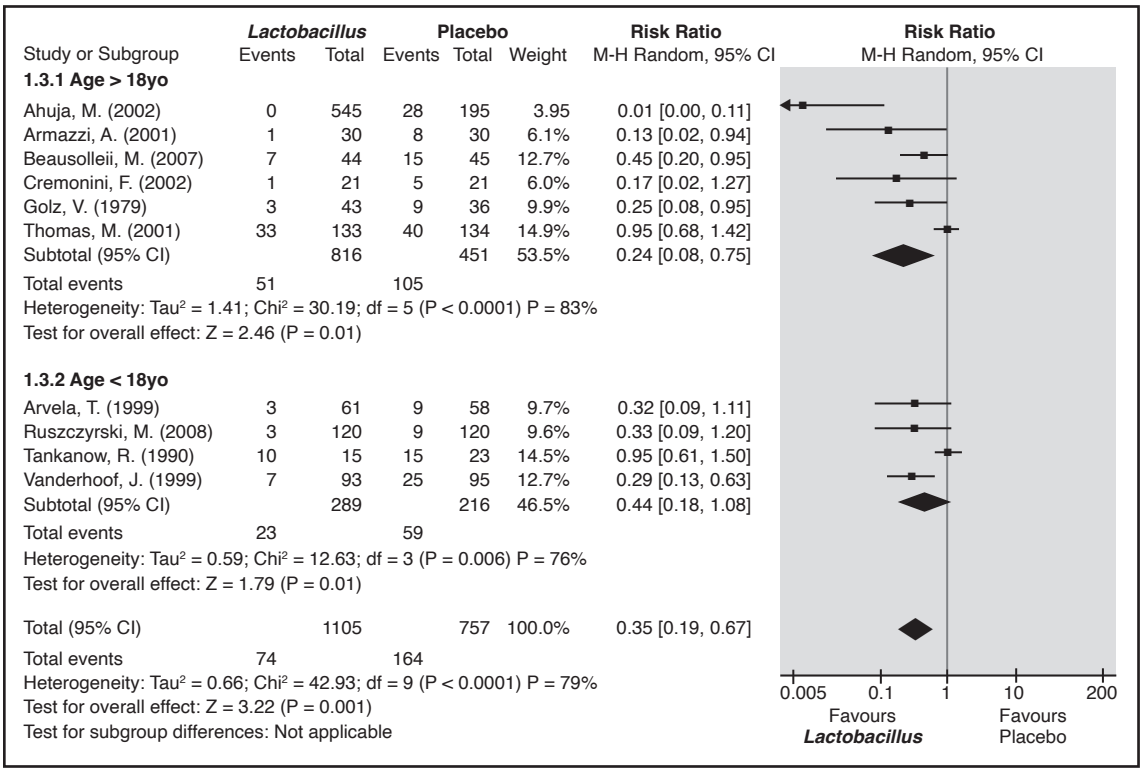
Lactobacillus
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H Random, 95% CI
M-H Random, 95% CI
1.3.1 Age > 18yo
Ahuja, M. (2002) 0 545 28 195 3.95 0.01 [0.00, 0.11]
Armazzi, A. (2001) 1 30 8 30 6.1% 0.13 [0.02, 0.94]
Beausolleii, M. (2007) 7 44 15 45 12.7% 0.45 [0.20, 0.95]
Cremonini, F. (2002) 1 21 5 21 6.0% 0.17 [0.02, 1.27]
Golz, V. (1979) 3 43 9 36 9.9% 0.25 [0.08, 0.95]
Thomas, M. (2001) 33 133 40 134 14.9% 0.95 [0.68, 1.42]
Subtotal (95% CI) 816 451 53.5% 0.24 [0.08, 0.75]
Total events 51 105
Heterogeneity: Tau² = 1.41; Chi² = 30.19; df = 5 (P < 0.0001) P = 83%
Test for overall effect: Z = 2.46 (P = 0.01)
1.3.2 Age < 18yo
Arvela, T. (1999) 3 61 9 58 9.7% 0.32 [0.09, 1.11]
Ruszczyrski, M. (2008) 3 120 9 120 9.6% 0.33 [0.09, 1.20]
Tankanow, R. (1990) 10 15 15 23 14.5% 0.95 [0.61, 1.50]
Vanderhoof, J. (1999) 7 93 25 95 12.7% 0.29 [0.13, 0.63]
Subtotal (95% CI) 289 216 46.5% 0.44 [0.18, 1.08]
Total events 23 59
Heterogeneity: Tau² = 0.59; Chi² = 12.63; df = 3 (P = 0.006) P = 76%
Test for overall effect: Z = 1.79 (P = 0.01)
Total (95% CI) 1105 757 100.0% 0.35 [0.19, 0.67]
Total events 74 164
Heterogeneity: Tau² = 0.66; Chi² = 42.93; df = 9 (P < 0.0001) P = 79%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable
0.005 0.1 1 10 200
Favours Lactobacillus
Favours Placebo

Figure 7. Forest plots.

CI = confidence interval; yo = years old.

From: Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy 2010;30:119-26.

XI. SUMMARY MEASURES OF EFFECT

A. Absolute Risk Measures
   1. Absolute risk (AR): Chance of an outcome occurring
      a. Table 6 example: ARRamipril = 14.0 (%) or 0.140
      b. Table 6 example: ARPlacebo = 17.8 (%) or 0.178
   2. Absolute risk difference (ARD): Difference in the absolute risk in exposed vs. unexposed
      a. The ARD can be an absolute risk reduction (ARR) or absolute risk increase (ARI) depending on the outcome.
      b. The ARD is the absolute difference between the incidence in the exposed group (experimental event rate or EER) and the incidence in the unexposed group (control event rate [CER]).
      c. Mathematically, the ARD = |EER – CER|
      d. Table 6 example: |EER (Ramipril) – CER (placebo)|
      e. Table 6 example: ARR: |0.14 – 0.178| = 0.038
   3. Number needed to treat (NNT)
      a. Another means to characterize changes or differences in absolute risk
      b. Definition: The reciprocal of the absolute risk reduction (ARR). It is the number of patients that need to be treated for a given period of time to see one patient have a positive outcome or prevent a negative outcome in one patient.
      c. NNT = 1/(ARR)
      d. Rounded to the next-highest whole number is the most conservative approach
      e. Applied to clinical outcomes with dichotomous data (e.g., yes/no, alive/dead, MI/no MI)
      f. Assumes the baseline risk is the same for all patients (or that it is unrelated to RR)
      g. Extrapolation beyond studied time points should not occur.
      h. NNTs should be provided only for statistically significant effects.
      i. Number needed to harm depends on the outcome being addressed.

B. Relative Risk Measures
   1. RR: Discussed earlier. Ratio of the risk in the exposed group to the risk of the outcome in the unexposed group
   2. Relative risk difference (RRD).
      a. A relative risk reduction (RRR) is calculated when the RR is less than 1 and a relative risk increase (RRI) is calculated when the RR is greater than 1.
      b. RRR can be calculated based on the ARR or the RR
         i. RRR = ARR/CER
         ii. RRR = 1 – RR
      c. RRI can be calculated based on the ARI or the RR
         i. RRI = ARI/CER
         ii. RRI = RR – 1
      d. Example using Table 6
         i. RRR = ARR/CER
         ii. RRR: = 0.038/0.178 = 0.21 (or 21%)

C. Absolute differences are more important than relative differences, though the authors of many clinical studies highlight the differences observed in trials with relative differences because they are numerically larger. Why? Larger numbers are more convincing to practitioners and patients. Most drug advertisements (both directly to patients and to health care professionals) quote relative differences.

D. NNT application
   1. HOPE (Heart Outcomes Prevention Evaluation) study (N Engl J Med 2000;342:145-53)
   2. Study evaluated the effect of ramipril on cardiovascular events in high-risk patients.
   3. Prospective randomized double-blind study
      a. 9297 high-risk patients received ramipril or matching placebo once daily for an average follow-up of 5 years.
      b. Primary outcome: Composite of MI, stroke, or death from cardiovascular causes
   4. Results shown in Table 6.

Table 6. Risk of Primary and Secondary End Points by Treatment Group

Outcome	Absolute Risk (%) Ramipril	Absolute Risk (%) Placebo	Relative Risk	RRR	ARR	NNT
Combined	14.0	17.8	0.79	0.21	0.038	27
Death from CV causes	6.1	8.1	0.75	0.25	0.02	50
Myocardial infarction	9.9	12.3	0.80	0.20	0.024	42
Stroke	3.4	4.9	0.69	0.31	0.015	67

ARR = absolute risk reduction; CV = cardiovascular; NNT = number needed to treat; RRR = relative risk reduction.

XII. REPORTING GUIDELINES FOR CLINICAL STUDIES

A. The Consolidated Standards of Reporting Trials (CONSORT)
   1. Initially published in 1996 and updated several times since—most recently, in 2010
   2. Created in an effort to improve, standardize, and increase the transparency of the reporting of clinical trials and to facilitate the improvement of literature evaluation
   3. Available at www.consort-statement.org/
   4. The CONSORT statement has been endorsed by several publications and published in these journals.
   5. The CONSORT statement
      a. The checklist: 25-item checklist pertaining to the content of the following:
         i. Title
         ii. Abstract
         iii. Introduction
         iv. Methods
         v. Results
         vi. Discussion
         vii. Other information
      b. The flow diagram: Intended to depict the passage of study participants through the randomized controlled trial
   6. Extensions of the CONSORT statement
      a. Design extensions
         i. Cluster trials
         ii. Noninferiority and equivalence trials
         iii. Pragmatic trials
      b. Intervention extension
         i. Herbal medicinal interventions
         ii. Nonpharmacologic interventions
         iii. Acupuncture interventions

c. Data extensions
   i. Patient-reported outcomes
   ii. Harms
   iii. Abstracts

B. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement
   1. Initially published in 2007
   2. "An international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies"
   3. Available at www.strobe-statement.org
   4. Endorsed by several publications and published in these journals
   5. The STROBE checklist: 22-item checklist, same basic concepts as the CONSORT checklist, with alterations germane to observational trials

C. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
   1. Established in 1996 (as QUOROM), renamed in 2009
   2. Evidence-based minimum set of items for reporting systematic reviews and meta-analyses
   3. Available at www.prisma-statement.org/
      a. The PRISMA checklist: 27-item checklist with alterations germane to systematic reviews and meta-analyses
      b. The PRISMA flow diagram: Four-stage diagram, depicting the flow of information through the systematic review
      c. The PRISMA explanation and elaboration document: Intended to enhance the use and understanding of the PRISMA statement

D. Enhancing the Quality and Transparency of Health Research (EQUATOR) Network
   1. International initiative to improve the reliability and value of medical research literature by promoting transparent and accurate reporting of research studies
   2. Does not have its own statements, but promotes the use of key reporting guidelines
   3. Many other statements regarding study types not addressed in the discussion related to CONSORT, STROBE, and PRISMA are listed on the EQUATOR network Web site (www.equator-network.org).

XIII. PHARMACOECONOMIC STUDIES

A. Cost-Minimization Analysis
   1. Differences in cost among comparable therapies are evaluated
   2. Only useful to compare therapies that have similar outcomes

B. Cost-Effectiveness Analysis
   1. Outcome: Clinical units or cost per unit health outcome (outcome examples: years of life saved, number of symptom free days, blood glucose, blood pressure, etc.)
   2. Useful to measure the cost impact when health outcomes are improved

C. Cost-Utility Analysis
   1. Assigns utility weights to outcomes so the impact can be measured in relation to cost (outcome example: quality-adjusted life-years)
   2. Compares outcomes related to mortality when mortality may not be the most important outcome

D. Cost-Benefit Analysis
   1. Monetary value is placed on both therapy costs and beneficial health outcomes.
   2. Allows analysis of both the cost of treatment and the costs saved with beneficial outcomes

XIV. SENSITIVITY/SPECIFICITY/PREDICTIVE VALUES

A. Sensitivity: Proportion of True Positives That Are Correctly Identified by a Test; a test with a high sensitivity means that a negative test can rule OUT the disorder

B. Specificity: Proportion of True Negatives That Are Correctly Identified by a Test; a test with high specificity means that a positive test can rule IN the disorder

C. Positive Predictive Value: Proportion of Patients with a Positive Test Result Who Actually HAVE the Disease

D. Negative Predictive Value: Proportion of Patients with a Negative Test Result Who Actually DO NOT HAVE the Disease

E. Example: Tables 7 and 8

Table 7. Relationship Between Test and Correct Diagnosis Identified by Disease

	Disease		
Test	**Disease Present**	**Disease Absent**	**Total**
Test positive	True positive (TP)	False positive (FP)	TP + FP
Test negative	False negative (FN)	True negative (TN)	TN + FN
Total	TP + FN	FP + TN	Total

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)
Positive predictive value = TP/(TP + FP)
Negative predictive value = TN/(TN + FN)
Positive likelihood ratio = sensitivity/(1 − specificity)
Negative likelihood ratio = (1 − sensitivity)/specificity

Table 8. Relationship Between Test and Correct Diagnosis Identified by Disease in a Published Study

	Disease		
Test	**Positive disease**	**Negative disease**	**Total**
Positive	231 (true positive)	32 (false positive)	263
Negative	27 (false negative)	54 (true negative)	81
Total	258	86	344

From: Drum DE, Christacapoulos JS. Hepatic scintigraphy in clinical decision making. J Nucl Med 1972;13:908-15.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
Recall bias is always a potential concern for case-control studies because of the amount of time that passes between the study and the drug "ingestion." Because risk factors were not included in the study design, this is of concern (Answer B is correct). Although a study may be susceptible to many types of bias, the other choices would not pose as much risk (if any) compared with recall bias (Answers A, C, and D are incorrect).

2. Answer: B
Internal validity is greatly jeopardized because the study is not designed to protect against this possible bias. In a sense, this design flaw jeopardizes external validity (how well a study apply to other patients with this condition/disease), but a lack of internal validity is most affected (Answer B is correct). The other answers can be adequately controlled for in the design and conduct of the study (Answers A, C, and D are incorrect).

3. Answer: B
Intention-to-treat analysis generally considers the approach, which gives the best estimate of use effectiveness (use under typical clinical trial conditions), whereas per-protocol analysis gives a better estimate of method effectiveness (use under ideal conditions) (Answer B is correct; Answer C is incorrect). Intention-to-treat analysis is the most common approach to data analysis for randomized controlled trials and may underestimate the treatment effect (Answer D is incorrect). Recall bias is not a concern with randomized controlled trials (Answer A is incorrect).

4. Answer: B
The CI of the difference in recurrence rate between the two groups includes zero; thus, there is no statistically significant difference between the two groups (Answer B is correct). Answer A is incorrect because the 95% CI contains zero and is therefore not statistically significant. Answer C is incorrect because not enough information is provided. Answer D is incorrect because all the above information can be determined without the benefit of reported p-values.

5. Answer: D
Answers A and C are incorrect calculations. Calculating the NNT to prevent one recurrence using twice-daily therapy is as follows: $0.044 - 0.029 = 0.015$ and $1/0.015 = 66.7\ldots67$; however, the NNT should not be calculated when the end point of interest is nonsignificant (Answer B is incorrect; Answer D is correct).

6. Answer: C
Answers A and B are incorrect because the margarine with ALA did not significantly reduce the risk of cardiovascular events (the 95% CI includes 1 [no difference in risk]). Answer D is incorrect because the p-value is not required for interpreting statistical significance when the 95% CI is provided. Answer C is correct because the p-value corresponds to the 95% CI.

7. Answer: A
Clinical trials are usually adequately powered to compare primary end points (Answer A is correct). Because Answer B is part of the composite outcomes, the study was likely not powered to detect this outcome independently. Similarly, even though the subgroup analysis was determined a priori, the study is not typically designed to have sufficient power to make this comparison (Answers C and D are incorrect).

8. Answer: D
Answers A and B are incorrect because each implies that one drug is more effective than the other. In this type of study design, neither drug is more/less effective. Answer C is incorrect because the CI of the OR does not include 1; thus, the finding is statistically significant at the 5% level, making Answer D correct.

Drug Information and Communication Strategies in Pharmacy

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Learning Objectives

1. Distinguish among primary, secondary, and tertiary drug information resources.
2. Outline the levels of evidence according to standard classifications.
3. Use the Population-Intervention-Comparator-Outcome-Setting/Study Design (PICOS) method to define a clinical drug information question.
4. Given a drug information question type, list key background questions and drug information resources to consider.
5. Describe strategies to maximize success of a PubMed search.
6. Review effective techniques for communicating drug information to patients and health care professionals.
7. Describe how to tailor drug information and provide effective education for individual patients and health care professionals.
8. Discuss strategies for assessing a patient's health literacy and demonstrating cultural sensitivity while providing drug information to patients.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Abbreviations in This Chapter

DOAC	Direct oral anticoagulant
FDA	US Food and Drug Administration
IVIG	Intravenous immunoglobulin
MEDLINE	Medical Literature Analysis and Retrieval System (MEDLARS) Online
MeSH	Medical Subject Headings
MI	Motivational interviewing
NVS	Newest vital sign
PICOS	Population-Intervention-Control-Outcome-Setting/Study Design
PPCP	Pharmacists' Patient Care Process
RCT	Randomized controlled trial
REALM	Rapid Estimate of Adult Literacy in Medicine
SAHL-S&E	Short Assessment of Health Literacy-Spanish and English
SAHLSA-50	Short Assessment of Health Literacy for Spanish Adults
SILS	Single Item Literacy Screener
TOFHLA	Test of Functional Health Literacy in Adults
USP	United States Pharmacopeia

1. While researching a question regarding the interaction between apixaban and cyclosporine, a pharmacist discovers the following article through a PubMed search: "Drug Interactions Between Direct-Acting Oral Anticoagulants and Calcineurin Inhibitors During Solid Organ Transplantation: Considerations for Therapy" (Expert Rev Clin Pharmacol 2019;12:781-90). Which best describes the type of medical literature this article is considered?
   A. Primary.
   B. Secondary.
   C. Tertiary.
   D. Quaternary.

2. A hospital institutes a new heart failure hospitalization treatment protocol. To assess quality improvement, 100 randomly selected patients treated under the new protocol are compared with 100 randomly selected, matched patients who received treatment under the previous protocol. Which design best describes this study?
   A. Case-control study.
   B. Cluster randomized controlled trial (RCT).
   C. Interrupted time series.
   D. Noncontrolled trial.

3. An attending physician asks a clinical pharmacist who practices in chronic disease management to research whether it is better to administer lisinopril twice daily instead of the typical once daily administration to control blood pressure in a 57-year-old patient being treated for hypertension. The patient also has a history of aortic dissection and dyslipidemia. Which PICOS question best describes the clinical question?
   A. P: Adult, I: Lisinopril Once Daily, C: Lisinopril Twice Daily, O: Blood Pressure, S: Community.
   B. P: Aortic dissection, I: Twice Daily, C: Once Daily, O: Blood Pressure, S: Outpatient.

C. P: Hypertension, I: Lisinopril Once Daily, C: Lisinopril Twice Daily, O: Quality of Life, S: Inpatient.

D. P: Hypertension, I: Lisinopril Twice Daily, C: Lisinopril Once Daily, O: Blood Pressure, S: Outpatient.

4. A pharmacist is performing medication reconciliation for a middle-aged male patient with obesity recently admitted to the ED for chest pain and shortness of breath. No firm diagnosis has yet been made. When discussing his prescription for amiodarone 200 mg orally once daily, he asks the pharmacist whether the drug has any adverse effects. Which question is most important for the pharmacist to ask next?

   A. Can you tell me a little more about why you are asking – do you think you've experienced a side effect?

   B. So that my records are as complete as possible, could you share your exact weight?

   C. This drug has many interactions, so please give me a full list of everything you take.

   D. This drug has many different side effects. Do you remember why your doctor started it?

5. A pharmacist performs a PubMed search to determine whether any articles describe a true increased risk of major bleeding from interactions involving direct oral anticoagulants (DOACs) and cyclosporine, a CYP3A4 and P-glycoprotein inhibitor in human clinical studies. The pharmacist combines the Medical Subject Headings (MeSH) terms for individual DOACs (combined with OR) with the MeSH terms for drug interactions AND cyclosporine. The search results in about 50 articles. Which is the best step the pharmacist could take to narrow the search results?

   A. Activate the clinical studies filter.

   B. Add drug class MeSH terms to the list of DOACs combined with OR.

   C. Add the MeSH term for major bleeding.

   D. Change to a non-MeSH term search approach.

6. A pharmacy manager is trying to determine how much physical space to have between the pharmacist and the patient during new-prescription counseling at a new pharmacy location. Which nonverbal communication concept is most used in this situation?

   A. Haptics.

   B. Proxemics.

   C. Kinesis.

   D. Chromatics.

7. A physician within a health network sends a message to an in-house clinical pharmacist asking to review a patient's medications for drug-drug interactions with the addition of a new HIV medication. The patient's next visit is in 2 weeks. Which would be the most appropriate form of communication for the pharmacist to use to respond to the physician?

   A. Standard message within the electronic health record.

   B. Urgent message within the electronic health record.

   C. Direct page to the physician with results.

   D. Telephone call to the physician's nurse.

8. A patient is working with the pharmacist to determine a correct dosing regimen for bolus insulin. The patient has had difficulty calculating the dose given the correction factor, so the pharmacist created a dosing chart with ranges for the patient (e.g., 150–200 mg/dL = 5 units). After a few months, the patient still cannot apply the simplified dosing regimen. Which most closely resembles this patient's National Assessment of Adult Literacy category?

   A. Below basic (level 1).

   B. Basic (level 2).

   C. Intermediate (level 3).

   D. Proficient (level 4).

9. A pharmacy team within an academic institution is looking for a health literacy assessment tool to use in a new study for patients in their outpatient clinic setting. The clinic serves many Spanish- and English-speaking patients, and the team is hoping to assess both literacy and numeracy. Pharmacists implementing the test will not have much time to complete the assessment, so they hope the test can be administered in 10 minutes or less. Which assessment would be most appropriate for the team to implement in this setting?

A. Rapid Estimate of Adult Literacy in Medicine–short form (REALM-SF).
B. Short Assessment of Health Literacy for Spanish Adults (SAHLSA-50).
C. Single Item Literacy Screener (SILS).
D. Test of Functional Health Literacy in Adults–short version (s-TOFHLA).

10. Which would likely be most effective to implement within a team of pharmacists to help increase their cultural sensitivity?
    A. Participate in a book club on new relevant literature.
    B. Compile resources from EthnoMed.org.
    C. Take online inventories to assess implicit biases.
    D. Incorporate the ETHNIC model into patient interactions.

11. A pharmacy team is looking to implement a study to assess patient adherence to antihypertensive drug regimens according to new guidelines. The pharmacy team has existing collaborative practice agreements for adjusting medications for hypertension. Which adherence tool would be most helpful to determine adherence to drug regimens for patients within the study?
    A. Patient Education Materials Assessment tool (PEMAT).
    B. "Adherence Estimator."
    C. Morisky questionnaire.
    D. Newest vital sign (NVS) assessment.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination: Content Outline.

2. Application of Evidence to Practice and Education
    a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Sub-task(s): 2.1.1 – 2.1.5, 2.1.7
    b. 2.3. Disseminate pharmacotherapy-related information to educate health care professionals, patients, and caregivers. Sub-task(s): 2.3.1 – 2.3.4

OVERVIEW

Pharmacists, especially those with responsibilities in providing direct patient care, are called on to have specialized knowledge and skills in drug information, also called medical or biomedical information. These skills involve fielding and assessing drug information questions from patients and health care professionals as well as researching their own inquiries; identifying situations when drug information resources are needed; selecting the most appropriate resources according to the question; effectively and efficiently using the resources; and determining an appropriate response. Communication of this information in a targeted, effective manner is imperative and is addressed in Part II of this chapter. Part I reviews the types of drug information resources available, levels of evidence, assessment of a drug information question, and search of secondary databases, with a focus on PubMed.

I. RETRIEVING DRUG INFORMATION

A. Types of Drug Information Resources

1. Primary: Primary literature consists of reports of original research, theories, ideas, and opinions. At the time of publication, primary literature was considered the most current information on the topic. For pharmacists providing drug information services, primary literature, specifically clinical research reports, is essential as the most detailed, specific, and original type of resource; however, the skills of interpreting, summarizing, evaluating, and synthesizing primary literature can be challenging, particularly with respect to biostatistics. This can be time-consuming, and accessing the primary literature can be expensive. Primary literature is usually presented as peer-reviewed articles published in scientific journals; however, other types of articles (e.g., clinical practice guidelines and review articles, which would be considered tertiary resources) are also published as peer-reviewed articles. Increasingly, preprints of primary literature that have not yet been peer reviewed or accepted for publication by a journal are available on the internet. Caution should be taken when using this information as part of a response to a drug information question.
2. Secondary: Secondary resources consist of indexing and abstracting databases that are used to organize primary and tertiary resources, especially those published in scientific articles. These resources do not provide original content, but a search will yield a list of citations (in the case of indexing systems) or citations with abstracts (in the case of abstracting systems). A link to the full-text article through open access sources (e.g., PubMed Central), the publisher, or the local institution's library may also be available to direct the user to more convenient access. The most relevant secondary resource for pharmacists is the MEDLINE (Medical Literature Analysis and Retrieval System [MEDLARS] Online), which can be freely searched using PubMed or searched with a subscription through EBSCO or Ovid. Secondary resources require individualized training and experience to perform effective and efficient searches. Table 1 summarizes the key secondary resources.

Table 1. Key Secondary Resources

Database	Publisher	Coverage	Topics
ClinicalTrials.gov	National Institutes of Health (NIH)	Clinical trial registry for privately and publicly funded clinical trials	Medications, biologic agents, dietary supplements, medical devices, and others
Cochrane Library	John Wiley & Sons	Cochrane systematic reviews, other systematic reviews (Cochrane Reviews), Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Clinical Answers	Medical interventions, diagnostics, conditions, alternative treatments; also includes a clinical trial registry and Cochrane Clinical Answers (CCA)
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	EBSCO	> 1000 medical journals	Nursing, allied health professions

Table 1. Key Secondary Resources *(cont'd)*

Database	Publisher	Coverage	Topics
ECRI Guidelines Trust	ECRI	Clinical practice guidelines similar to coverage in the former National Guideline Clearinghouse	Clinical practice guideline citations, snapshots, briefs, and appraisals
Embase	Elsevier	MEDLINE journals + 2900 additional journals as well as coverage of abstracts from > 10,000 conferences	Similar to MEDLINE with greater coverage of international journals, known for having less lag time between publication and indexing than MEDLINE
Google Scholar	Google	Any scholarly material (mainly from scientific journals) available online	All scientific disciplines, biomedical or otherwise, may identify free full text articles not identified by other secondary resources, results organized by number of citations
International Pharmaceutical Abstracts (IPA)	Clarivate Analytics, access available through OVID, ProQuest, and EBSCOhost	> 800 peer-reviewed journals with relevance to pharmacy practice	Drug therapy topics from basic pharmaceutical information to clinical practice, with clinical study abstracts broken down by pharmacist-relevant content (e.g., dose, dosage form)
LexisNexis (now Nexis Uni)	LexisNexis Academic & Library Solutions	> 60,000 legal, news, and public records sources	Medical, legal, and business news information, current events
MEDLINE	National Library of Medicine (NLM)	> 5000 peer-reviewed journals published in > 40 languages	Basic sciences, health sciences, medicine, pharmacy, nursing dentistry, veterinary, other allied health professions
Trip Database	Trip Database Ltd.	All RCTs and systematic reviews from MEDLINE, + all other content from the top 500 MEDLINE peer-reviewed journals, + other sources (e.g., Cochrane Collaborative, guideline developers, regulatory agencies, eBooks)	Similar to MEDLINE; searchable using PICO terms (see text that follows) and filterable by evidence type, freely available online

RCT = randomized controlled trial.

3. Tertiary: Tertiary resources are compendia that provide convenient, easily usable information that has been synthesized and summarized from the primary literature. These include electronic drug and medical information databases, references and textbooks (whether print or electronic), and types of journal articles such as clinical practice guidelines and review articles. Systematic review articles that also include a meta-analysis of pooled data can be considered tertiary (because they are synthesized from the primary literature) or primary (because they generate new results). Like the primary literature, the strongest tertiary sources are prepared by content experts and undergo a peer review process. They should be closely scrutinized for appropriate attribution of primary sources as well as updating time because there is often publication lag between the time of content development and the time of publication, especially in the case of books. Tertiary resources should always be the first step in a systematic search for drug information because they provide good content and may provide a current and comprehensive answer as well as direct the user to key primary literature on the topic. However, depending on the question and findings, secondary and primary sources may also be needed.
    a. There are many different types of review articles, ranging in rigor from basic narrative reviews or summaries prepared without formal methodology to true systematic reviews that follow rigorous,

predetermined methods and seek to be comprehensive. Rapid reviews use systematic methods to a greater extent than narrative reviews, although less than systematic reviews because of the efforts to shorten the development process. Whatever the style used in the review article, it is important for the reader to critically evaluate the methods in terms of the resources searched to identify, select, evaluate, and synthesize the evidence.

b. Table 2 describes commonly used general tertiary resources. All resources describe FDA-approved medications (prescription and non-prescription), though, as noted, some also cover internationally approved products. All address labeled and off-label uses, except for the resources that only provide access to prescription information (i.e., DailyMed, FDA website, *Physicians' Desk Reference*) or speak to non-clinical information (i.e., United States Pharmacopeia [USP]).

Table 2. Key Tertiary Resources

Resource	Publisher	Print	eBook	Electronic	Mobile	Notes/Content
American Hospital Formulary Service (*AHFS*) *Drug Information*	ASHP	X		X	X	Provides a high level of detail regarding supporting clinical evidence; also available on Lexicomp
Clinical Pharmacology	Elsevier Gold Standard			X	X	Medication and medication class monographs. Additional tools include interaction, IV compatibility checker, product identification tool, and patient education (English and Spanish); interactions tool covers food and tobacco interactions; provides drug-specific information from Beers Criteria and Institute for Safe Medication Practices; searchable by adverse reaction with detailed adverse reaction and extensive product availability information
DailyMed	NLM			X		FDA-approved package inserts (i.e., prescribing information) available as a downloadable PDF document or online viewing, links to information about the medication available on ClinicalTrials.gov, FDA pages (e.g., MedWatch, Safety Recalls), MedlinePlus, and PubMed
DrugBank	OMx Personal Health Analytics			X		Focus on medicinal chemistry, pharmacology, pharmacokinetic, and pharmacogenomics information
Facts and Comparisons/eFacts and Comparisons	Wolters Kluwer Clinical Drug Information	X		X	X	Medication and medication class monographs covering topics similar to the prescribing information, well-suited for community pharmacy practice; includes comparison tables and tools for drug identification, interactions, IV compatibility, and clinical calculators; offers in-depth off-label use evaluations; provides electronic access to *Review of Natural Products*; also available through Lexicomp
Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care	APhA	X	X			Overview of nonprescription therapeutics (including drugs and dietary supplements) organized by body system, includes treatment algorithms
Index Nominum	Medpharm Scientific Publishers			X		Provides chemical and nomenclature information for medications available in > 130 countries; available through Micromedex

Table 2. Key Tertiary Resources *(cont'd)*

Resource	Publisher	Print	eBook	Electronic	Mobile	Notes/Content
Lexicomp (Lexicomp Online and the *Drug Information Handbook*)	Wolters Kluwer Clinical Drug Information	X		X	X	Includes a variety of sub-databases focused on topics such as natural products, special populations, toxicology, allergy and idiosyncratic reactions, and pharmacogenomics; includes drug monographs, product identification, IV compatibility, patient information handouts based on their literacy level (e.g., Basic, Beyond Basic), and interaction tools (especially good for drug–laboratory interactions), as well as information about which guidelines address the medication and expanded qualitative information describing key adverse drug reactions and effects of importance; also available through UpToDate
Martindale: The Complete Drug Reference	Pharmaceutical Press	X		X		Provides monographs on > 6000 medications, with special coverage of international drugs, as well as some special products (e.g., diagnostics, radiopharmaceuticals, supplements, veterinary); also available through Micromedex, Lexicomp
Merative Micromedex	Merative			X	X	Known for coverage of off-label uses, pharmacokinetics, and pharmacology; includes tools for checking a variety of interaction types (especially drug-food, drug-tobacco, and drug-alcohol), IV compatibility, need for pharmacokinetic dose adjustments, and toxicology; includes access to Red Book for pricing information; also available through DynaMed, conversational search available through Watson Health artificial intelligence
PDR and Prescribers' Digital Reference	ConnectiveRx			X	X	Compilation of FDA-approved prescribing information, with special print editions for herbal products, nonprescription drugs, ophthalmic drugs, and supplements
Drugs@FDA	FDA			X	X	Provides comprehensive FDA-approved information, including a full history of drug labeling, communication, and medication guides (though may not be as up to date as DailyMed); the FDA website (outside Drugs@FDA) includes updates on safety information (e.g., recalls, adverse drug events), the Orange Book for therapeutic equivalence, and the Purple Book for information on biologic products, including biosimilars
USP Dictionary of USAN (U.S. Adopted Names) and International Drug Names	U.S. Pharmacopeial Convention	X		X		Provides information on chemical, generic, and proprietary names as well as chemical information such as structure and molecular weight

APhA = American Pharmacists Association; ASHP = American Society of Health-System Pharmacists; FDA = U.S. Food and Drug Administration; IV = intravenous(ly); PDR = Physicians' Desk Reference; NLM = National Library of Medicine.

c. The following tertiary resources are more specialized for providing specific types of drug information:
   i. Adverse effects and reactions – FDA Adverse Event Reporting System, FDAble (searches adverse events reported to MedWatch and other FDA reporting systems), *Meyler's Side Effects of Drugs, Side Effects of Drugs Annual* (provides an annual update on new data regarding adverse drug reactions), Clin-Alert (provides bimonthly updates on adverse drug reactions, interactions, and other safety concerns), *Drug-Induced Diseases* (provides an overview of detection and management of diseases and conditions related to medication use)
   ii. Compounding - *Handbook on Injectable Drugs* (compatibility and stability of compounded parenteral products, Trissel's 2 Clinical Pharmaceutics database available in Clinical Pharmacology, eFacts and Comparisons, Lexicomp, and Micromedex), *King Guide to Parenteral Admixtures* (compatibility and stability of compounded parenteral products), *Trissel's Stability of Compounded Formulations* (compounding information for nonsterile compounded products), *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients* (compendium of published compounding formulations)
   iii. Dietary supplements – Dietary Supplement Label Database (maintained by NIH Office of Dietary Supplements), *Natural Medicines* (searchable database that provides comprehensive information on over 1400 dietary supplements)
   iv. Interactions – *The Top 100 Drug Interactions* (pocket guide to managing the most common drug-drug interactions), *Stockley's Drug Interactions* (in-depth information on drug-drug and other drug interactions)
   v. Medical information – UpToDate (brief outlines of diagnosis and management of specific disease states and patient populations), DynaMed (brief outlines of diagnosis and management of specific disease states and patient populations); these can also be great resources for identifying key clinical practice guidelines in a particular area (DynaMed, as well as Lexicomp itself, provides a listing of clinical practice guidelines in each drug monograph), ClinicalKey.
   vi. Pharmacogenomics – Pharmacogenomics sub-database in Lexicomp (provides recommendations on genetic testing and scientific information on genes of interest), PharmGKB (searchable database covering relevant drug labeling, scientific content, and clinical practice guidelines, including those from the Clinical Pharmacogenetics Implementation Consortium)
   vii. Pregnancy and lactation – *Drugs in Pregnancy and Lactation* (in-depth literature analysis of drug safety, available on eFacts and Comparisons and Lexicomp), LactMed (electronic database addressing drug-milk penetration–related safety concerns, available as a mobile app and part of the NCBI Bookshelf), *Catalog of Teratogenic Agents* (includes medications as well as other products), *Medications and Mothers' Milk* (provides information about drug-milk penetration and safety)
   viii. Special populations – *Harriet Lane Handbook* (provides an overview of treating common pediatric conditions, including a drug formulary with brief pediatric monographs; available electronically through *Clinical Pharmacology*), Red Book: Report of the Committee on Infectious Diseases (standards of care for managing infectious diseases in pediatric patients), AIDSInfo (freely available at NLM), NeoFax (available electronically through Micromedex).
   ix. Toxicology – *Goldfrank's Toxicology Emergencies* (therapeutic management of toxicology cases by drug and drug class), TOXNET (now broken out and distributed into a set of databases for toxicology searches; some yield primary literature vs. tertiary information), LiverTox (freely available at NLM)
   x. Veterinary products – *Compendium of Veterinary Products* (compilation of approved monographs), *Plumb's Veterinary Drug Handbook* (extensive monographs covering labeled and off-label uses for veterinary products), *Small Animal Clinical Pharmacology and Therapeutics* (overview of drug-based management of disease states and drug formulary monographs)

Patient Case
Questions 1–5 pertain to the following case.

1. A staff pharmacist at XYZ pediatric hospital receives a medication order for a 12-year-old female patient for intravenous immunoglobulin (IVIG). The patient is currently admitted to the hospital for acute myocarditis unrelated to rheumatic, septic, or toxic causes. The patient has no other discernible reason to receive IVIG, but the pharmacist is unfamiliar with this off-label use. Which tertiary reference would best be checked to gather more information about this topic from an off-label use perspective?
   A. AHFS Drug Information.
   B. DailyMed.
   C. Drugs@FDA.
   D. Manufacturer-provided prescribing information.

B. Levels of Evidence
   1. Levels of evidence, or the hierarchy of evidence, is a system for rating the primary literature according to the design, while considering methodological quality and validity, to help inform applicability to patient care. Levels of evidence are typically based on the types of design outlined in Table 3. This table generally orders the evidence from lowest to highest strength.

Table 3. Types of Research Design Represented in Levels of Evidence

Domain	Type	Example
Descriptive: Evidence that simply shares anecdotal experiences involving events that occurred during patient care. This evidence lacks a formal, prospective method	Case report: A full description of events involving an unusual, novel, or interesting single patient case. In drug information or pharmacoepidemiology, this often involves previously unreported medication use or safety concerns such as adverse reactions and interactions. This is typically accompanied by a review of the literature	Description of a previously healthy 16-year-old male adolescent who received tissue plasminogen activator for the treatment of frostbite, providing new insight into dosing, concomitant medications, and patient outcomes in the adolescent population (Air Med J 2011;30:39-44)
	Case series: Similar to a case report, but involves several patients. Patient data may be aggregated, but typically, individual patient-level results are provided	Description of five Japanese patients who received ponatinib for the treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia, with individual cases and some aggregate results described, suggesting a potential therapeutic concentration (Int J Hematol 2021;114:199-204)

Table 3. Types of Research Design Represented in Levels of Evidence *(cont'd)*

Domain	Type	Example
Observational: Evidence that has a formal, prospectively planned method but is not considered experimental (i.e., there is no interventional agent administered to the sample of patients). This evidence is often associated with pharmacoepidemiology and pharmacovigilance	Cross-sectional study: Examines a sample of patients at a given time point to examine the prevalence of risk factors and/or outcomes of interest (also called prevalence studies). This study design, when applied in pharmacoepidemiology, can often be thought of as analogous to survey research but involves medication use and outcomes patterns rather than responders' perspectives. This is considered the lowest level of observational study because there is only a single measurement per patient	Evaluation of blood pressure control and description of common medications used within a sample of patients undergoing hemodialysis from a single dialysis center, as a quality improvement initiative in order to identify rates of uncontrolled blood pressure and explore the prevalent medications (Medicina (Kaunas) 2021;57:590)
	Case-control study: Identifies a sample of patients who have experienced an outcome of interest and matches them to a second group of similar patients who have not experienced that outcome. Investigators then look into secondary data sources (e.g., medical documentation, billing records) to determine the prevalence of various risk factors (or exposures) to determine whether any were more or less associated with the outcomes of interest. This is considered stronger than a cross-sectional study because of the presence of a control group as well as because it has measurements from at least two time points. This study design is helpful for examining rare outcomes because it "zooms in" on the outcome of interest and efficiently examines several risk factors	Female patients older than 45 who experienced a bone fracture were matched in a 1:4 ratio to randomly selected similar patients who did not experience a fracture, using population-based data sources. Differences in exposure to hormonal drugs, including estrogens and progestins, specifically, and adherence were compared between the groups (Maturitas 2021;146:1-8)
	Cohort study: This type of study is basically the opposite of a case-control study. A sample of patients with a risk factor or exposure of interest are identified and matched, manually or using propensity scoring, with a control group of similar patients who lack the specific risk factor or exposure. Then, patients are followed over time in a forward-moving fashion to measure the development of outcomes of interest. This can be done from a past time point forward to a more proximal past time point or the present (i.e., a retrospective or historical cohort) or beginning at the present and moving into the future (i.e., a prospective cohort). This creates conditions similar to a RCT, though there is no true randomization that places the study at risk for the impact of confounding variables. This study can be conducted when an experimental study would be unethical or unlikely to achieve adequate power, as in a large, population-based cohort study designed to examine safety outcomes (often considered a gold standard for pharmacoepidemiology). Finally, a dynamic cohort study involves patients who move in and out of cohorts depending on changing circumstances, such as if they were taking a medication for a finite duration (i.e., while on the medication, they would be in the exposed group; while off, they would be in the control group)	Patients receiving DOACs or warfarin who were at high risk of bleeding were propensity matched, then compared pairwise (e.g., apixaban-dabigatran, apixaban-rivaroxaban, apixaban-warfarin) to compare rates of stroke, systemic embolism, and major bleeding. Patients were originally enrolled in 2012 and followed through 2015 (JAMA Netw Open 2021;4:e2120064)

Table 3. Types of Research Design Represented in Levels of Evidence *(cont'd)*

Domain	Type	Example
Interventional: Also called experimental or quasi-experimental (i.e., not a true randomization), interventional studies involve a formal, preplanned method, like observational studies. Unlike observational studies, however, interventional studies involve administering an intervention to a patient who otherwise would not have seen one	Noncontrolled trials: Although less common in recent years, interventional studies involving a single group of patients who all receive the intervention of interest may be identified through a search of the literature, especially when research drug information questions are on topics that are not under active study. These may also be conducted when a placebo control would be unethical yet there is no clear standard of care. This design is highly susceptible to placebo effect and relies on a comparison of patients at end of study with baseline in a paired comparison	Patients in an ICU who were not responding to dexamethasone were treated with a preplanned protocol of cyclosporine + favipiravir for COVID-19. Lengths of ICU stay, hospital stay, and mortality were measured (Int Immunopharmacol 2021;99:108043)
	Interrupted time series: Also called use of a historical control, interrupted time series is most commonly used in practice-based or programmatic research when investigators seek to implement a practice change and compare its impact with the previous conditions. This is considered a quasi-randomized design because the sample of patients is compared with a historical control group of patients who did not receive the intervention, rather than with a true concurrent control group	A pharmacist-led antimicrobial stewardship initiative including education, prospective audit, and pre-authorization through patient-specific antimicrobial "timeouts" was used to reduce ertapenem use for ESBL Enterobacteriaceae. Institutional ertapenem use was compared before intervention with after intervention (BMC Infect Dis 2021;21:823)
	Non-equivalent control group: This is another quasi-randomized study in which group membership is determined by a procedure that is not truly random, such as when patients are offered the opportunity to self-select into one group or the other (introducing risk of selection bias) or when groups are preformed on the basis of patient location (e.g., by clinic, hospital, geographic region). In this scheme, also called a cluster randomized trial, patients are placed in groups according to their location of enrollment so that everyone at the location is placed in the same group	Patients received 1- or 3-day prophylactic antibiotics at the time of catheter removal after radical prostatectomy. Duration of prophylaxis was randomized at the surgeon level, rather than the patient level, so that all patients receiving care from a particular surgeon were assigned to the same group (J Urol 2021;206:662-8)
	RCT: The gold standard, highest level of primary evidence for studying efficacy; RCTs minimize the risk of both placebo effect (through control) and confounding variables (through randomization) as well as selection bias (also through randomization). Use of appropriate blinding and intention-to-treat principles help reduce the risk of other types of bias. Details of RCT interpretation and evaluation can be found in another chapter	A double-blind, randomized, placebo-controlled trial in which adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease received empagliflozin 10 mg, empagliflozin 25 mg, or placebo: Patient groups were compared using a composite outcome of cardiovascular death, myocardial infarction, and stroke (N Engl J Med 2015;373:2117-28)

DOAC = direct oral anticoagulant; ESBL = extended-spectrum β-lactamase.

2. Reference books, clinical practice guidelines, and drug information resources use these domains and evidence types, as well as others, to describe levels of evidence supporting their recommendations in various ways. In addition to the study design, the quality of the individual studies is incorporated into many schemes. Finally, many schemes incorporate language speaking to other matters such as magnitude of effect, confidence in the effect, and strength of the authors' recommendation or endorsement. This process is also called "evidence grading." Table 4 provides example grading schemes (these are not intended to be comprehensive; many grading systems exist). Note that the grading definitions may not be fully described in the resource (especially in the case of clinical practice guidelines), but instead housed in a companion or method document.
3. One final key strategy for grading comes from the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method. This grading system is used by many clinical practice guidelines.
    a. First, quality of evidence is rated. The initial level of confidence is determined according to whether the supportive evidence is from randomized trials (high) or observational studies (low). Confidence level is raised or lowered depending on risk of bias, confounding variables, and other flaws. The final level is then defined as high, moderate, low, or very low.
    b. Next, strength of the recommendation is determined considering quality of evidence, risk-benefit, patient perspectives, and cost. Strength of recommendation is defined as strong (applies to most situations) or weak (applies to many or some situations).

Table 4. Example Grading Schemes

Category	Source	Level	Description
Clinical Practice Guidelines	American Heart Association (AHA) (number + letter)	I	Intervention is recommended, indicated, or useful
		IIa	Intervention is reasonable, useful, effective, or beneficial
		IIb	Intervention may be reasonably considered; usefulness is unknown or not well established
		III: No Benefit	Intervention is not recommended
		III: Harm	Intervention is potentially harmful or should not be performed
		A	Meta-analysis of strong RCTs or at least one strong RCT
		B-R	Meta-analysis of moderate RCTs or at least one moderate RCT
		B-NR	Meta-analysis or at least one nonrandomized trial, observational study, or registry study
		C-LD	Meta-analysis, RCT, nonrandomized, observational, or registry studies with limitations; physiologic evidence
		C-EO	Anecdotal, expert opinion
	American Diabetes Association (ADA) (letter only)	A	Clear evidence from strong RCTs, compelling nonexperimental evidence, or supportive evidence from several RCTs
		B	Supportive evidence from strong cohort or case-control studies
		C	Supportive evidence from studies lacking good control, including RCTs or observational studies with flaws or bias, descriptive studies, or conflicting evidence
		E	Anecdotal experience or expert consensus

Table 4. Example Grading Schemes *(cont'd)*

Category	Source	Level	Description
DI Databases	Lexi-Drugs (letter only)	A	Consistent high-quality RCTs or overwhelming evidence from another source; unlikely to be changed by further evidence
		B	RCTs with inconsistent results, flaws, or other limitations or strong evidence from other sources; may be changed by further research
		C	Observational studies, anecdotal experience or flawed RCTs; uncertain effect estimates
		G	Use is recommended in a clinical practice guideline (not mutually exclusive with A–C)
	Micromedex (number + letter)	I	Recommended to initiate therapy
		IIa	Recommended to initiate therapy in most cases
		IIb	Recommended to initiate therapy in some cases
		III	Not recommended
		A	Findings from well-designed meta-analyses of RCTs or several large, well-designed RCTs
		B	Meta-analyses of RCTs with conflicting results, small or flawed RCTs, or observational studies
		C	Descriptive studies, expert opinion, or consensus
Reference Books	Drug Information: A Guide for Pharmacists (number only)	I	Well-conducted (e.g., controlled, randomized), powered interventional studies
		II	Well-conducted but underpowered interventional studies
		III	Well-conducted (e.g., controlled, randomly identified), prospective observational studies
		IV	Well-conducted, retrospective observational studies
		V	Flawed interventional or observational studies (e.g., no control group, nonrandomized)

DI = drug information; EO = expert opinion; LD = limited data; NR = nonrandomized; R = randomized; RCT = randomized controlled trials.

Patient Case *(cont'd)*

2. The staff pharmacist at XYZ pediatric hospital located an endorsement that IVIG has an off-label use in pediatric myocarditis, with the dose of 2 g/kg intravenously given as a single dose over 24 hours (limited and variable efficacy data available), as well as a statement from the AHA that the medication has been used but that study results have been mixed (grade III (no benefit)/B-NR). Which does the grading most suggest?
   A. Do not use the intervention because it causes harm.
   B. Intervention can be considered, according to evidence from a well-designed randomized controlled trial (RCT).
   C. Intervention can be considered, according to anecdotal expert opinion.
   D. It is not recommended, with the highest level of evidence from non-RCTs.

3. The pharmacist at XYZ pediatric hospital also identifies an observational study in which patients admitted to the hospital for acute myocarditis during a 3-year period were grouped according to whether they received IVIG. The two groups were compared at the time of discharge to evaluate survival outcomes and left ventricular function recovery. Which design best classifies this study?
   A. Case-control study.
   B. Interrupted time series.
   C. Noncontrolled trial.
   D. Retrospective cohort study.

C. Assessing a Drug Information Question

1. The Seven Step Modified Systematic Approach to Drug Information is a systematic method designed to help pharmacists provide the best possible answer to drug information questions, especially those that are patient-specific. It is highly complementary to the more contemporary Pharmacists' Patient Care Process (PPCP) but addresses some considerations to drug information responses as a patient care activity.
2. Steps 1 and 2 of the Seven Step Approach are to determine the demographics of the requestor in order to understand their background and perspectives and to gather background information about the question. Gathering information about the question includes a thorough investigation of the events that led to the question (e.g., why is it being asked?) and the gathering of patient-specific details (e.g., who is the question about?). This provides greater context for the responder and helps them generate a more patient-specific response. These steps align with the Collect step of the PPCP.
3. Step 3 of the Seven Step Approach is to determine the true question being asked, which aligns well with the Assess step of the PPCP. Many times, the initial question will be vague and generally phrased, and it is essential to incorporate the information gathered through steps 1 and 2 to provide an answer to the true question. For example, in one case, a man in his mid-20s presented at a community pharmacy to ask what the pharmacist recommended for the treatment of heartburn. In reality, the requestor was there asking the question on behalf of his wife, who was experiencing moderate heartburn symptoms at bedtime, while lying down, and after eating spicy meals and chocolate during the first trimester of her pregnancy. Thus, the true need greatly differed from how it may have initially appeared.
4. Often, it can help to categorize the question before planning the search strategy (step 4 of the Seven Step Approach) because this can help inform the background questions being asked as well as the resources consulted. Table 5 summarizes potential key background data to consider, as well as notable tertiary resources according to question type.

Table 5. Key Background Data and Resources by Question Type

Question Type	Background Data	Tertiary Resources
Adverse events	Whether an adverse event has occurred, severity, resolution, adverse event signs and symptoms, dose, current and recent medications (always considering prescription, nonprescription, dietary supplements) and doses, steps taken to manage the event, known history of allergies, adverse reactions, adverse effects, intolerances, timing of event relative to medication administration and initiation	*Clinical Pharmacology*, Micromedex, Lexi-Drugs, Prescribing Information, *Side Effects of Drugs Annual*, *Drug-Induced Diseases*, FDAble
Dosing	Age, weight, indication, organ function (e.g., renal, hepatic), pharmacogenomic profile, administration or tolerability issues, current and recent medications	Facts and Comparisons eAnswers, Lexi-Drugs, Micromedex, *Clinical Pharmacology*, prescribing information (as well as other sources that provide access to these sources, such as DynaMed and UpToDate)
Drug selection/ off-label uses	Same data as for Dosing + a history of allergies, adverse reactions, adverse effects, and intolerances; other chronic disease states, any recent diagnostic tests.	Clinical practice guidelines, review articles, reference books, *AHFS*, Lexi-Drugs, Micromedex, *Clinical Pharmacology*, DynaMed, UpToDate

Table 5. Key Background Data and Resources by Question Type *(cont'd)*

Question Type	Background Data	Tertiary Resources
Interactions	Whether an active interaction is suspected, whether an adverse event has occurred, current and recent medications and doses, timing of administration, treatment duration, steps taken to manage the interaction	Facts and Comparisons eAnswers, Lexicomp, Micromedex, *Stockley's Drug Interactions*, *Natural Medicines* (drug-dietary supplement only)
Nonprescription drugs/dietary supplements	Same data as for Dosing/Drug Selection + a patient history of self-management, whether use was recommended by a health care professional or whether they were aware of patient interest/use, symptoms being managed, current dose and how administered if already taking, specific manufacturer/product being used, reason for a nonprescription/supplement agent	Clinical Pharmacology, *Natural Medicines*, Lexicomp (*Natural Products* sub-database), Micromedex (AltMedDex), review articles
Pediatrics/geriatrics	Age/gestational age, sex, height, weight, body mass index, nutritional status, organ function (especially in older adults), administration/tolerability, swallowing issues, taste issues (especially in children), baseline cognition, activities of daily living, level of independence	*Pediatric and Neonatal Dosing Handbook* (and Lexicomp sub-database), NeoFax/Pediatrics (a Micromedex sub-database), *Geriatric Dosing Handbook* (and Lexicomp sub-database), Clinical Pharmacology, *Harriet Lane Handbook*, resources for potentially inappropriate medications in older adults (e.g., Beers Criteria), Red Book
Pregnancy/lactation	Current trimester and/or number of weeks pregnant; infant and/or gestational age; indication for the medication; organ function; breastfeeding timing and frequency; history of allergies; adverse reactions, adverse effects, and intolerances; pregnancy history, including how the medication/condition was managed during pregnancy and before pregnancy	*Drugs in Pregnancy and Lactation*, *Medications and Mothers' Milk*, Lexicomp Pregnancy and Lactation sub-database, LactMed, REPROTOX (on Micromedex), clinical practice guidelines

a. Once sufficient background data have been gathered and the true need has been articulated, the PICOS approach can help concisely articulate a clinical question as well as generate searchable terms that can be used to search secondary sources, like PubMed. Each question will not necessarily have a term for each category. It can help to break down clinical questions as follows:
   i. **P**: patient, population, or problem. What is the key disease state being treated? Are there other patient-specific dimensions that need to be considered?
   ii. **I**: intervention or interest. What is the key medication, or other intervention, that is the focus of the question? This is often the more experimental or exploratory medication involved in the question.
   iii. **C**: comparator or control. If the question involves efficacy or safety, is a pertinent comparator or control medication, or otherwise, involved in the question? This is often more the usual care involved in the question or what is currently being received by the patient (vs. the intervention that represents the novel agent being considered).
   iv. **O**: outcomes. What effects of the medication, efficacy or safety, are of particular interest in the question?

v. **S**: setting. What health care settings are relevant to the question? Is it acute, ambulatory, or something more specific? Note – the S can also refer to "study design" and can be used in this way when a specific level of evidence is of greatest relevance (e.g., RCT for efficacy evaluation, population-based cohort study for safety evaluation).

5. Step 5 of the Seven Step Approach is to evaluate, analyze, and synthesize the information that is found. In this context, "evaluate" refers to a critical appraisal of the resource or piece of evidence for strengths, limitations, generalizability, clinical significance, and impact. "Analyze" refers to systematic gathering of key data points from each source so that they can be compared. "Synthesize" refers to putting all the findings together, highlighting commonalities but also pointing out areas where resources might differ.
6. Steps 6 and 7 of the Seven Step Approach are formulating and communicating a response (aligning with the Implement step of the PPCP) and performing a follow-up (aligning with the Follow-Up step of the PPCP). These steps are highlighted in the second section of this chapter.

D. Searching PubMed

1. PubMed is the most essential secondary database for pharmacists because it is freely available from any location with internet access and covers a large scope of scientific journals. The general skills needed for effective PubMed searches are transferable to other secondary databases, though certainly the details will vary. The largest component of PubMed is MEDLINE (described earlier in the text), but PubMed also searches other sources and provides links to PubMed Central. PubMed Central provides full-text access to open access articles. PubMed also searches Bookshelf, which provides full text to a variety of biomedical-related book chapters and other resources.
2. Articles are indexed in MEDLINE using MeSH terms. Searching PubMed using MeSH terms helps improve search specificity (i.e., results are generally more focused on the topic of interest). Using MeSH terms should remove erroneous results not directly focused on the topic of interest. MeSH terms also help improve search sensitivity (i.e., results will also provide better coverage of the relevant articles on the topic). This is because MeSH terms link synonyms as "entry terms" so that individual synonyms do not have to be individually searched. For example, the entry terms for heart failure include a variety of current and past expressions of this disease state, including congestive heart failure, myocardial failure, and heart decompensation. Articles that used these other terms would still result through the literature search. The net effect of using MeSH terms is that fewer results generally appear. Embase has its own standard terms known as Emtree terms, based on MeSH but optimized to be more intuitive.
3. From the PubMed homepage, the easiest way to perform a search using MeSH terms is to select "MeSH Database". Terms should be individually searched through the MeSH search bar. If an exact match is searched, the entry for the MeSH term will populate. If it is not an exact match, a list of potential terms will result. Terms can then be selected by checkbox with the "Add to Search Builder" button used to add to the PubMed Search Builder.
4. In the entry for each MeSH term, sub-term checkboxes can help the user customize the search (though these may make the search too specific). It is also possible to use the term as a MeSH "major" term, which implies extra relevance of the term to the article. The entry terms and term hierarchy are provided, giving users an idea of whether they have selected a term that is at the appropriate level of specificity.
5. If second, third, or more terms are added to the search, the appropriate Boolean operator should be selected to construct an appropriate search. In a two-term search, AND would result in articles indexed to both terms. OR would result in all articles indexed to each term. NOT would result in all articles indexed to the first term unless they are also indexed to the second term. Caution is advised with using NOT because of the risk of unnecessarily excluding articles of relevance. Once the desired terms are added to the search builder, clicking "Search PubMed" provides the initial search results. It is always good to check the search (available in the bar at the top of the page) to make sure the parentheses have terms organized in a logical way, especially when using OR and/or NOT for searches involving more than two terms. Often, initially searching with more than two or three terms can lead to an overly

specific set of results and risk omitting key articles. When less than 100 articles or so appear in the search results, it may be better to filter the results (see the text that follows) than to add more terms.

6. The PubMed interface also provides automatic term mapping. When a user searches from the main search bar using simple terms, PubMed automatically maps the entered terms to MeSH terms if an entry term is detected. It also searches the entered term in all fields.
    a. This approach can be helpful because the sensitivity benefits of MeSH terms (i.e., linking synonyms) are realized with the broadened scope of the "all-fields" search, if desired. This approach assumes AND as a Boolean operator unless other operators are used. This can save time and help ensure more potentially related articles are located. However, because it searches for the term in "all fields," results may be less specific.
    b. This approach can also help ensure that recently published articles result in the search (because MeSH indexing takes 3–6 months), as well as find articles that, for whatever reason, were not indexed to the expected terms. If the primary goal is to focus on recently published studies, the date filters provide an easy way to focus the results of a simple search. If the reason is more to find articles that were not indexed to the expected terms, the advanced search tool can be used to combine the simple search with the MeSH search using NOT in order to focus on results from the simple search.
7. PubMed defaults to ordering using a "best match" scheme. In systematic searches, it help to change the display option to reverse chronological.
8. Many filters are available to help ensure the most relevant articles appear in the search results. These include free text availability (note: "free full text" means free for all and does not consider institutional library holdings), article types (e.g., clinical studies, practice guidelines, meta-analyses), language, patient age, and species. Filtering for English language articles relevant to human subjects can help remove erroneous results from clinical searches. Additional filters beyond the default settings can be accessed using a button at the bottom of the filter list. When less than 25 articles appear in the results, it may be best to begin manually reviewing the results rather than trying to filter further, to avoid over-filtering. The age filters can be particularly helpful when looking for studies with representation of various age groups that do not necessarily have to be conducted exclusively in that group. Custom date ranges can be applied. Subheadings (e.g., dosing and administration) and MeSH major terms can also be used to help focus results.
9. PubMed keeps track of searches so that users can always go back and reference recent searches by selecting "Advanced" under the search bar. Past searches listed under "History and Search Details" can be added back into the query. They can also be combined using the Boolean operators.

Patient Case *(cont'd)*

4. Which of the following PICOS terms correctly describes the clinical question at XYZ pediatric hospital?
    A. P – Acute myocarditis
    B. I – Pediatric
    C. C – IVIG
    D. O – Hospitalization

5. Which of the following strategies could the pharmacist at XYZ pediatric hospital use in their search PubMed in order to improve sensitivity of results?
    A. Add filters for article types and publication date.
    B. Combine related terms for acute myocarditis using "OR."
    C. Use the MeSH database to search with MeSH terms only.
    D. Use the regular PubMed interface with automatic term mapping.

II. COMMUNICATING DRUG INFORMATION

A. General Communication Techniques and Strategies
   1. Build rapport with the patient.
      a. Good rapport with patients and providers is built on mutual trust and respect, allows open and honest communication, and creates an environment in which information is less likely to be withheld.
      b. If possible, the AIDET tool should be used as a framework to introduce yourself to the patient, caregiver, or provider and to let them know what to expect. AIDET was created for the hospital setting but can be modified and applied to several situations (https://www.studergroup.com/aidet).
         i. **A**cknowledge: Greet the patient by name. Make eye contact, smile, and acknowledge family or friends in the room.
            (a) Warmly greet patients using their preferred mode of address.
            (b) Use their first name only if invited to do so or after permission is given.
            (c) Make sure the current setting is an appropriate place where full attention can be given by both the patient/caregiver and the provider.
            (d) Acknowledge the purpose of the encounter. "The physician was hoping we could review the proper use of your asthma medication."
         ii. **I**ntroduce: Introduce yourself with your name, skill set, professional certification, and/or experience.
         iii. **D**uration: Give an accurate time expectation for the current session or when to expect other steps to occur.
         iv. **E**xplanation: Explain step-by-step what to expect next, answer questions, and let the patient know how to contact you, such as a telephone number or email address.
            (a) Focus on a mutual agenda for the visit. "You are hoping to review the key points of taking your blood thinner and see if there are any drug-drug interactions with your current medications. What else would you like to discuss today?"
            (b) On closing, summarize joint decisions and verify next steps. "You've decided to start taking your chlorthalidone in the morning and your lisinopril at night to help get the most of your blood pressure medications. What else do you plan to do to help get your blood pressure under control?"
         iv. **T**hank you: Thank the patient and/or caregiver. You might express gratitude to them for choosing your pharmacy or hospital or for their communication and cooperation. Thank family members for being there to support the patient.
   2. Use nonverbal communication.
      a. Body language and tone are important foundations for developing a patient/provider relationship.
      b. Because of varying natures of pharmacy practice, several factors must be considered as practices are developed. For example, a pharmacist who is meeting with patients one-on-one in a hospital room or in a clinical setting may need to arrange the room in a particular way to maximize outcomes and minimize chances of poor communication. By considering "proxemics", the pharmacist may self-position close to the door for a quick exit in the case of an urgent call or page. In general, this approach is the best practice in most settings, but it may not always be possible to arrange the room in advance. Another example would be for a team to create standards on dress and attire when interacting with a patient or colleague, such as wearing matching clothes, removing jewelery, or ensuring outfits are not wrinkled or dirty. This type of nonverbal communication is based on consideration of "objectics" as an approach to improve outcomes. Table 6 defines and explores various concepts of nonverbal communication.

Table 6. Nonverbal Communications

Concept	Definition	Questions to Consider with Patients, Caregivers, or Providers
Proxemics	Use of physical distance between people	- What types of activities are most appropriate? - What are the cultural differences in physical location? - How close to sit/stand next to the patient/provider?
Chronemics	Use of time	- How long did the patient/provider have to wait? - Was the patient on time? - How long is the clinic visit? - What are the cultural differences on time?
Oculesics	Use of eye contact	- Is the amount of eye contact appropriate? - What are the cultural differences on looking directly in the eyes or looking away? - Is looking at the computer/device appropriate during an encounter? - What is this saying about the person's attitude, honesty, intelligence, and feelings?
Haptics	Use of touch	- Does this touch come across as superficial or demeaning? - Is this communicating empathy, warmth, or acceptance? - What are the patient/provider boundaries with physical touch? - Is this something the provider is comfortable doing?
Kinesis	Use of body movements	- Are the gestures consistent with words/emotions? - What will pointing or other gestures convey? - Where are the gestures aimed? (direction of pointing) - What does thumbs-up/thumbs-down mean and is this accepted in all cultures? What are other gestures that are not acceptable in certain cultures? - Which direction is the provider's back pointed toward regarding the patient?
Objectics	Use of objects	- What does the provider's clothing show about them? (e.g., wrinkled vs. dirty, jewelry, formal vs. informal, use of laboratory jacket) - What patient educational materials are used or available for patients? - How is the waiting area arranged and organized? - What reading materials are offered? - Are there any distracting uses of objects (e.g., clicking of pen, tapping of foot, beeping from telephone)
Vocalics	Use of vocal tone and pitch	- Does communication focus on quality over quantity (e.g., clarity, inflections, emphasis) - What volume is appropriate, and does this change between cultures?

3. Engage in active listening.
    a. React to ideas and not the person (e.g., not judging a patient for not taking their medications, but seeking out their reasoning behind the nonadherence).
    b. Read the patient's body language.
    c. Listen to the patient's tone of voice as well as the patient's words.
    d. Ask for clarification as needed, and seek understanding of the patient's motives.
    e. Write down notes of the patient's thoughts and values at the same time as writing down follow-up questions to ask after the patient finishes talking.
    f. Permit silence in the interaction by allowing the patient to pause and think or allow for silence between questions and thoughts.

4. Show empathy.
    a. Showing empathy helps patients know they have an advocate as they ask three important questions subliminally within their mind: "What's going on?" "What's going to happen next?" "How am I being treated?" Table 7 provides several types of showing empathy.

Table 7. Showing Empathy

Action Used	Purpose	Examples
Reflecting	To show understanding of a person's feelings	- "You seem very upset" - "You've had a really tough time getting answers to your questions" - "You wish you knew more about this vaccine"
Encouraging	To convey interest and to encourage the person to continue talking and sharing	- "Please tell me more about that" - "These are difficult topics to talk about. Your openness and honesty in discussing this with me is really brave."
Summarizing	To review progress and to pull together important ideas and facts	- "To make sure I heard you right, it sounds like you are saying…" - "Before we move on, let me try to sum up what you are telling me" - "These are some of the big ideas you've brought up"
Clarifying	To help clarify what is said, to get more information, and to help the speaker see other points of view	- "You have had a really hard time making healthy choices with your foods. What has worked for you so far?" - "Where did you experience those muscle pains?" - "How often has this happened?"
Restating	To show listening and understanding of what is being said and to help the speaker clarify what they are saying	- "It sounds like you would like to try all your oral medications options before switching to insulin. Is that right?" - "Your lack of trust with the government has you second-guessing whether you want to get a vaccine"
Validating	To acknowledge the worthiness of the other person	- "You have done a really good job of keeping track of your blood pressure readings this past month" - "You have had a lot of really good ideas on how you might be successful in quitting smoking"

    b. Empathy generally avoids "clichés" (e.g., "If I read between the lines…"), immediately trying to fix or minimize the problem ("the righting reflex"), being empathetic without responding empathetically, or confusing empathy with becoming too personally involved.
5. Choose key questions at key times.
    a. Framing the question: Allows the person to know why the question is being asked and be prepared for what is to come. "To get the most out of your HIV medications, I may need to ask a few questions and they may be difficult to answer."
    b. Use of prompts: Allows all involved to know what to expect and know where to focus attention (e.g., pointing finger at an object) and helps finish thoughts or ideas. "You mentioned you were going to send a drug information question. When would you like this to be answered?"
    c. Probing questions: Ask for more focused or clarifying information. "In what ways?" "Tell me more about…" "How did that make you feel when…"
    d. Open-ended questions: Create deep responses with more detail, especially early in conversations; however, these can take more time to employ. "How do you take this medication?" "What are you hoping to answer with this conversation?"
    e. Closed-ended questions: May allow for further clarification when specific details are needed in a time-efficient manner but may reduce patient openness and are more passive. "How many tablets do you take?" "Do you still take this medication?"

f. *Use* mnemonics like **SCHOLAR-MAC** (symptoms, characteristics, history, onset, location, aggravating factors, remitting factors, medications, allergies, conditions) to assess a patient's problem and symptoms systematically and comprehensively. In most cases, it may not be appropriate to ask a question for each factor, but this standardized approach can help a practitioner to avoid omitting important information.

Table 8. Using the SCHOLAR-MAC Acronym to Collect Patient Information

A patient asks, "Can you help me figure out why I have all this swelling?"	
SCHOLAR-MAC	**Example Questions**
Symptoms	"What is your main concern?"
Characteristics	"Describe the swelling. How much worse is it now than normally?"
History	"Have you had swelling in the past?"
Onset	"When did you notice this starting?"
Location	"Where is the swelling located?"
Aggravating factors	"What makes the swelling worse? Do you notice a difference in the morning vs. when you have been on your feet all day?"
Remitting factors	"What has made the swelling better?"
Medications	"What medications have you tried to help with the swelling?"
Allergies	"What allergies do you have to medications?"
Conditions	"What other medical conditions do you have?"

g. Avoid leading questions. These types of questions can force a patient or provider to answer in the manner expected of them instead of what is true and accurate to them. "You take your Genvoya with food, right?" "You don't miss any doses, do you?"

h. Avoid compound questions. In most cases, a patient or provider will only remember the last question asked of them and can forget the first part of the question. Instead, break down these complex questions into individual and concise questions. "How are you doing with your snacking, and what can you be doing better to get more fruits and vegetables into your diet?"

i. Avoid circling back to already answered questions or duplicate questions because this repetition can show a lack of listening or engagement in the conversation.

j. Use the **BATHE** (background, affect, troubling, handle, empathy) procedure when dealing with a patient's problems when there is an emotional component or when the problem significantly alters quality of life.

Table 9. BATHE Procedure

BATHE	**Example Questions**
Background	"What is going on in your life?" assesses the circumstances surrounding the encounter, but if the patient has already discussed this, move on to "Affect"
Affect	"How do you feel about that?" helps the patient elicit their emotional response. This can help the patient identify their own feelings in a situation
Trouble	"What troubles you the most about this?" focuses on the symbolic meaning behind the patient's situation
Handling	"How are you handling that?" helps determine the patient's ability to respond to the situation
Empathy	"That must be very difficult for you" reflects understanding and validates the patient's response is reasonable, given the circumstances
For more information, visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181054/pdf/i1523-5998-001-02-0035.pdf.	

B. Tailoring for Individual Patients and Health Care Professionals
   1. Communicate drug information with patients or caregivers.
      a. Motivational interviewing (MI) is effective to initiate, guide, and maintain goal-oriented thoughts and behaviors.
         i. The purpose of MI is to create a conversation about change to strengthen personal motivation for and commitment to a specific goal or targeted change.
         ii. The "Spirit of MI" strengthens rapport and positive outcomes for patients by encouraging collaboration, the 4 "A's of acceptance" (autonomy, absolute worth, affirmation, accurate empathy), evocation, and compassion. Effectively using the components of MI should center around these principles to empower patients and reinforce that they are an important part of their own care.
         iii. The "Four Fundamental Processes of MI" help create a framework for effectively implementing MI for patients. Table 10 discusses some practical ways to use these processes when engaging with patients and practitioners.

Table 10. The Four Fundamental Processes of Motivational Interviewing

Process	Purpose	Components/Examples
Engaging	Process of establishing a mutually trusting and respectful helping relationship	- Reflective listening: "You are worried what this new diagnosis will mean for your family": "You've grown up avoiding medications and now the doctors you respect are advising you to take medications" "If you knew your medications were working, you wouldn't miss as many doses throughout the week"
Focusing	Process of strategically centering both the provider and the patient goals	- Summary statements: "Here's what I've heard. Let me know if I've missed anything…" "Let me see if I understand…" - Agenda mapping: "Which aspect of diabetes do you want to focus on today?" "We've talked about some of the things you can do during the day to cut back on smoking. Let's talk about medications that can improve your chances of quitting"
Evoking	Process of drawing out the patient's thoughts while empowering the patient to take ownership of their goals (the "bridge" to planning)	- Elaboration: "Tell me more." "In what ways" - Query extremes: "What is the worst thing that could happen if you make this change?" "What is the best thing…?" - Looking forward: "If you were 100% successful in making this change, what would life look like in 10 years?" - Looking backward: "What was life like before you had a drinking problem?" - Encourage "change talk": "Why would you want to make this change?"
Planning	Process that allows the patient to create their own plan by promoting self-efficacy and autonomy	- Elicit-provide-elicit: "What do you know about…? (elicit)" "Do you mind if I share some information about…? (provide)" "What thoughts do you have about this now? (elicit)" - Timing key questions: "Given what you've told me, what do you think you will do next?" "What's your next step in order to …?" - Asking permission: "Taking this medication correctly can be complicated. Do you mind if I give you a few pointers and tips to get the most out of taking it?"

b. Other key components of MI
    i. Encourage ***change*** talk. This is any form of communication that moves the patient toward an attitude of change, though it may not always be appropriate if the patient is unwilling to consider the change. "If you knew avoiding fast food would decrease your risk of disease, you would consider changing up your lunch habits." "What is the best reason for you to make this change right now?"
    ii. Avoid and soften ***sustain*** talk. The patient may get trapped in communication while nothing is accomplished and circle back to their original thought process, though this can help build rapport for patients with resistant behavior. "You can't see yourself giving up smoking." "Why haven't you quit smoking yet?"
    iii. Dancing with ***discord***. Sustain talk is about resistance in making a targeted behavior change, whereas discord is about conflict within a personal relationship. It is important to repair the relationship by maintaining the Spirit of MI using reflections to diffuse a situation (e.g., "You are angry with our pharmacy team"), shifting focus (e.g., "You've got strong opinions about that topic. Maybe we should talk about something else?"), and/or emphasizing personal choice (e.g., "We can't make you take your medications. We just want to give you the information so that you can make the best choice for yourself").
    iv. Avoid the ***righting reflex***. The patient may not feel validated or cared about if the provider is trying to fix their problem or their way of thinking. Instead, focus on autonomy and allowing the patient to make the decision. "I'm sorry you are going through a very hard time. I'd really like to hear more about what you are going through."

2. Communicate drug information with health care professionals using the PPCP.
    a. *Collect* information to better assess the drug information opportunity (e.g., demographics, situation, background, history of present illness, "SCHOLAR-MAC" information).
        i. Define the problem or issue. "What is the patient's chief concern, or the problem being addressed?"
        ii. Clarify the problem or request additional information such as blood tests or information from the patient history.
        iii. Determine the health care professional's timeline for when they need an answer shared back with them, and if applicable, ask for a preferred mode of delivery.
    b. *Assess* the situation to plan for a successful resolution.
        i. If necessary, consider why this situation occurred in anticipation of asking clarifying questions or requesting additional information. "Is this likely an oversight or an intended choice by the prescriber?"
        ii. Assess and analyze the therapeutic alternatives in pursuit of the best recommendation for resolving the situation. "What is the strength of the evidence to support each recommendation?" "How might the recommendation change depending on the additional patient information requested?"
        iii. Decide on the best audience and recipient to better frame the recommendation. "What will they know or want to know?"
            (a) Discipline: Physicians, nurse practitioners, and physician assistants generally have a different level of knowledge of therapeutics and evidence-based medicine.
            (b) Generalist vs. specialist: "Is this therapeutic recommendation within or outside their area of specialty?"
            (c) Academic vs. nonacademic: "Is this information directly applying to a patient, or is it academic in nature?"

(d) Personality of the provider: "Is this provider open to recommendations from an outside source?" "Will they process this recommendation and consider the implications, or directly apply the recommendation?"
(e) Differences in communication styles: "Does this provider prefer more detail, or do they prefer simple communication?" "Will they be more likely to read a fax or listen to a voicemail?"

c. *Plan* and *implement* communication of drug information to the health care professional.
   i. Choose an appropriate vehicle to communicate with the provider depending on the urgency and nature of the drug information.
      (a) Fax: May send to provider's office if issue is not time-sensitive and if relationship with provider is not well established
      (b) Email: May be viable when the provider/pharmacist relationship is established but the issue is not time-sensitive
      (c) Telephone/video call: Can be used if the patient care issue requires immediate attention or further clarification is necessary. This may include talking to the provider's health care team (e.g., nurse, medical assistant, receptionist) for gathering further information.
      (d) Low-priority message: Can be used if the pharmacist/provider shares electronic health records with non-urgent patient care situations
      (e) Page/high-priority message: Can be used during time-intensive and urgent situations and if an issue needs to be resolved immediately to prevent harm to patient
   ii. Deliver the message to the provider while being clear, complete, concise, timely, professional, and organized.
      (a) Identification of self and greeting should catch attention with level of urgency: "Good morning, Dr. Smith; it has come to my attention…" "Hello Nurse Karen, we have been treating a mutual patient and…"
      (b) Give a solution with appropriate verbiage according to the strength of the recommendation. "I strongly recommend we…" "If deemed appropriate by both you and the patient, we might consider…"
   iii. Provide a rationale and offer evidence to support the recommendation (see Tables 3 and 4).
d. *Follow up* with the health care professional or patient to make sure the problem or drug information situation is resolved. Be prepared to modify your recommendation in response to new information or a challenge from the provider.

3. Tailor verbal and written communication styles to patients and health care professionals.
   a. Effective communication with providers generally follows the "SBAR" format:
      i. **S**ituation – Briefly describe the situation or the patient problem.
      ii. **B**ackground – Add necessary information to understand the problem.
      iii. **A**ssessment – Provide an assessment of the problem, such as cause and severity.
      iv. **R**ecommendation – Make recommendations to address or resolve the problem.
      v. Table 11 highlights the application of SBAR in a situation for which a pharmacist must communicate a recommendation to a provider regarding a bleeding event with aspirin. This format can be tailored in several ways depending on the nature of the interaction and can be presented in both verbal and written communications.

Table 11. Example Use of SBAR for Patient-Specific Recommendation

Patient Case Example: Bleeding risk with aspirin	
SBAR	**Example Communications**
Situation	"Good morning Dr. Jacobs. I am communicating today regarding a mutual patient, Jane Doe, and a concern for increased bleeding with her current aspirin medication"
Background	"Jane is a 76-year-old who currently takes aspirin 81 mg daily for primary prevention of a heart attack or stroke. She also currently takes warfarin (pharmacy-to-dose) for atrial fibrillation together with other medications for hypertension and hypothyroidism. She has no history of coronary artery disease or other self-stated disease states"
Assessment	"Given the patient's age and concurrent warfarin therapy, adding aspirin would greatly increase the risk of serious bleeding. Moreover, patients similar to Jane in the ASPREE trial had an increased risk of bleeding and mortality without much added benefit after adding aspirin 81 mg daily for primary prevention"
Recommendation	"I recommend discontinuing aspirin 81 mg daily as soon as possible and continuing with therapeutic dosing of warfarin alone"

SBAR = situation, background, assessment, recommendation.

Information from: Agency for Healthcare Research and Quality (AHRQ). TeamSTEPPS® Program. Available at http://teamstepps.ahrq.gov/; Institute for Healthcare Improvement (IHI). SBAR Tool: Situation-Background-Assessment-Recommendation. Available at www.ihi.org/resources/Pages/Tools/SBARToolkit.asp.

b. Telephonic communication
   i. Ask for or look up the patient's or provider's preferred telephone number, and contact him or her at that number.
   ii. Before discussing specific patient information, do the following:
      (a) Confirm the identity of the recipient or caller, and if necessary, ask for date of birth or other verifying demographic information.
      (b) Verify the patient has time to talk ("Would you have a few minutes to talk about…"). Including a simple question like this at the beginning of any interaction can help build trust and rapport with patients because it shows that their time is valuable and respected.
   iii. Protect patient privacy while using discretion with details. Limit details left in messages. "This is _____, the pharmacist at XYZ pharmacy, with a message for (patient name). Please call me back at (number)" (e.g., do not discuss confidential information).
   iv. If possible, note whether the listed telephone number is a home phone, personal cell phone, or work phone.
   v. Use the teach-back method to verify the correct understanding of messages ("To make sure I communicated this correctly, can you please repeat back what I told you to do?").
   vi. For efficiency and consistency, consider developing documentation templates for common encounters in the electronic medical record (e.g., requests for refills, anticoagulation test results, intravenous antibiotic results).
   vii. Document the content and results of the communication in the patient's medical record.
c. Email etiquette: See Box 1 for methods to refine email etiquette when communicating with patients, providers, or other health care professionals.

Box 1. Things to Avoid in a Formal Email to a Patient or Health Care Professional

- Forwarding chain mail
- Replying to all senders when reply is "I agree" and there are several recipients
- Expressing strong emotion
- Using email to circumvent having a conversation on a difficult subject matter
- Requesting a read receipt on every email
- Using all-capital letters
- Nonstandard fonts (anything except Calibri, Times New Roman, Arial)
- Spelling errors
- Sarcasm and jokes
- Forwarding messages that the sender would want to be kept private
- Claiming others' ideas as one's own
- Being extremely lengthy and redundant
- Forgetting to answer the original sender's questions if a reply
- Emoticons
- Drifting off-topic

Email Etiquette. ASHP.org. https://www.ashp.org/pharmacy-technician/about-pharmacy-technicians/advanced-pharmacy-technician-roles-toolkits/medication-history-technician-toolkit/email-etiquette?loginreturnUrl=SSOCheckOnly; 10 Rules of Pharmacy Email Etiquette. Pharmacy Times. March 2021. Available at https://www.pharmacytimes.com/view/10-rules-of-pharmacy-email-etiquette; Silberman L. 25 Tips for Perfecting Your Email Etiquette. Inc.com. June 2010. Available at www.inc.com/guides/2010/06/email-etiquette.html.

d. Telehealth use
    i. *Telehealth* is the use of electronic information and telecommunication technologies to support or promote long-distance clinical health care, patient and professional health-related education, public health, and health administration. Example technologies include video conferencing, telephonic communication, store and forward imaging, and remote patient monitoring.
    ii. *Telepharmacy* is defined in the Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (Model Act) as "the provision of pharmacist care by registered pharmacies and pharmacists located within U.S. jurisdictions through the use of telecommunications or other technologies to patients or their agents at distances that are located within U.S. jurisdictions" (https://nabp.pharmacy/resources/model-pharmacy-act/).
    iii. When using telehealth or telepharmacy, it is important to know whether these services can be billed through a patient's insurance and financial justification can be provided for services rendered. Some third-party organizations, such as OutcomesMTM and other telehealth servicers, work to bridge the gap between payers and patients and can provide better access to care for patients. During the COVID-19 pandemic, many states, payers, and organizations have expanded payment for telehealth services in an attempt to improve accessibility of health care professionals, including pharmacists.
    iv. For helpful tips on communicating with patients, caregivers, and other health care providers, see https://www.pharmacist.com/Practice/Practice-Resources/Telehealth for more information.

C. Assessing Health Literacy
    1. Health literacy: Degree to which individuals have the ability to obtain, process, and understand the basic health information and services needed to make appropriate health decisions
        a. Four literacy domains identified: reading, writing, speaking, and basic numeracy. These are generally what is considered when thinking of "general literacy," but others exist such as scientific domain (e.g., basic purpose and function of various organs), cultural domain (e.g., beliefs, customs, and social identify), and civic domain (e.g., applying health information to make decisions regarding general public policy).

b. According to a report of adults by the Program for the International Assessment of Adult Competencies completed in 2017, only 14% scored at the highest levels of literacy, and only 10% scored at the highest levels of numeracy in the United States.
c. The National Assessment of Adult Literacy categorizes health literacy into four performance levels:
    i. ***Below basic*** (level 1): Around 14% of the population or about 40 million Americans. These adults may be able to interpret short, simple text to perform routine tasks. However, those at level 1 have trouble matching information or identifying numbers to use in mathematical problems.
    ii. ***Basic*** (level 2): An additional 22% (about 50 million American adults) can solve routine mathematical problems or make simple inferences. However, people with level 1 or level 2 skills would find it difficult to interpret a dose chart on an over-the-counter cold medication to calculate the correct dose for a child. Yet, some individuals at level 2 may be able to look at a very basic and simplified correction factor scale and add units of insulin to their normal bolus dose, although a more complex scale may be difficult for them to interpret.
    iii. ***Intermediate*** (level 3): About 53% of the population can summarize text; find and apply facts from denser text; and identify and apply information to solve arithmetic calculations. People in level 3 may be able to determine a healthy weight from a BMI chart or interpret instructions from prescription and over-the-counter drug labels.
    iv. ***Proficient*** (level 4): Only 12% of the population can analyze and integrate several pieces of information or solve more abstract or multistep mathematical problems. Furthermore, the population in level 4 could likely calculate the correct dose required of a liquid solution from a recommendation made in milligrams per kilogram.

2. Risk factors for low or inadequate health literacy
    a. Include (but are not limited to) those older than 65, those with less than a high school education, those with low income, those for whom English is a second language, and immigrants and refugees. However, the largest group numerically consists of White individuals.
    b. The presence of risk factors alone does not reliably identify low or inadequate health literacy. It is vital to assess each individual patient using validated and systematic approaches.
3. Health literacy can be assessed in several different ways to tailor appropriate patient-specific educational sessions. Table 12 details assessment tools that have been developed for research or clinical settings. Some of the tools listed are more academic and research-focused and may be long and unpractical to administer to patients in practical, whereas others serve a more clinical role by being readily available and rather quick to administer.

Table 12. Summary of Common Health Literacy Assessment Screening Tools

Tool	Description	Clinical Pearls
REALM	List of 66 common words related to anatomy or illnesses where adults read and pronounce words; takes 3 min to administer and score	- Commonly used in research studies - Does not directly measure comprehension of health information but has been highly correlated with reading comprehension (e.g., reading-grade level) - Primarily assesses reading skills but not numeracy or mathematical ability - REALM-SF is a shorter version (7-item word recognition) to provide clinicians with a valid, quick assessment and has excellent agreement with REALM

Table 12. Summary of Common Health Literacy Assessment Screening Tools *(cont'd)*

Tool	Description	Clinical Pearls
SAHLSA-50	Involves reading 50 words where a choice between two distractors is used to indicate understanding; takes 3–6 min to administer	- Is commonly used in research studies - Is based on the REALM, but of importance, results are not similar to REALM results - Is intended for adults who speak Spanish but is not a Spanish translation of REALM - Users who may want to compare the health literacy of English and Spanish speakers are recommended to use SAHL-S&E
TOFHLA	Consists of 50 reading and 17 numeracy items involving common medical situations; takes up to 22 min to administer	- Commonly used in research studies - Results are categorized into inadequate, marginal, or adequate levels of health literacy - Spanish versions are available for both the full and the shorter versions of the TOFHLA - Scores between men and women varied on the shorter versions - s-TOFHLA is a shorter version that uses only 36 of the reading questions and 4 numeric calculations, takes 7 min to complete
NVS	Contains six questions to assess interpretation of a standard nutritional label; takes 3 min to administer	- Is commonly used in clinical assessments - Assesses both literacy and numeracy (includes arithmetic calculations) - Is available and validated in both English and Spanish, with both versions correlating with the TOFHLA
SILS	Is only one question: "How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor of pharmacy?"; takes seconds to 1 min to administer	- Commonly used in clinical assessments - Response scale is from 1 (never) to 5 (all of the time); response of > 2 (sometimes, often, always) has a 54% sensitivity and 83% specificity for identifying inadequate health literacy - Was developed for the Veterans Affairs clinics, but has been tested in the primary care population and is easy to integrate into clinical practice - More reliably identifies those at risk of low/inadequate health literacy compared with confirming those with adequate health literacy; stronger correlation with s-TOFHLA and REALM in detecting inadequate compared with marginal health literacy - Does not assess numeracy
SAHL-S&E	Consists of 18 terms to test comprehension and pronunciation of health-related terms; takes 2–3 min to administer	- Commonly used in clinical assessments - New instrument consisting of similar tests in English and Spanish with good reliability and validity - For each "term," a key word with a related meaning and distractor is used to test the subject's comprehension as well as their pronunciation of health-related terminology

NVS = newest vital sign; REALM = Rapid Estimate of Adult Literacy in Medicine; SAHL-S&E = Short Assessment of Health Literacy-Spanish and English; SILS = Single Item Literacy Screener; TOFHLA = Test of Functional Health Literacy in Adults.

Agency for Healthcare Research and Quality (AHRQ). Health Literacy Measurement Tools (Revised). Content last reviewed November 2019. Available at https://www.ahrq.gov/health-literacy/research/tools/index.html; North Carolina Program on Health Literacy. Literacy Assessment Instruments. Content last reviewed July 2022. Available at www.nchealthliteracy.org/instruments.html.

Additional health literacy tools available at http://healthliteracy.bu.edu/.

4. Applying health literacy to drug information and providing accurate information while creating print and audiovisual patient educational materials are important for tailored messaging to patients. Specific action items and descriptions for various forms of communication are available using the patient education materials assessment tool (PEMAT) at https://www.ahrq.gov/health-literacy/patient-education/pemat.html.
    a. An assessment tool can be used for both printable materials (PEMAT-P) and audiovisual materials (PEMAT-A/V). In these assessments, materials are presented as 24 items for printable materials and 17 items for audiovisual materials, for which the the assessor can mark "Disagree" or "Agree" or, in some cases, "Not Applicable". These "items" are categorized in domains of "understandability" (with subtopics of content, word choice and style, use of numbers, organization, layout and design, and use of visual aids) and "actionability". Results are calculated and percentage of understandability and actionability can be compared between resources.
    b. Within each of the domains and topic, items are critically assessed and feedback for applying correct forms of communication are given. For example, materials with "use of numbers" would have numbers that are clear and easy to understand. A label reading "Take 1 tablet in the morning and 1 tablet at night" is easier to understand than "Take twice daily". In regards to actionability, materials should clearly identify an action a user can take. Material stating "patients who do not use a reminder tool typically forget to take their medications" is not as actionable as the text, "Use a pillbox or alarm on your phone to help you remember to take your medications".

Patient Case

Questions 6 and 7 pertain to the following case.

The pharmacist is meeting with L.S., a 61-year-old Hispanic woman who is working with the clinical pharmacy team to manage her warfarin dosing. The pharmacist believes that the patient has issues with adherence. This has led to supratherapeutic INRs and even a hospitalization because of excess bleeding. L.S. tells the pharmacist, "I just don't trust these pills. Sometimes, I don't feel right, and I won't take them, but I don't want to have a clot, so I'll take a few more the next time."

6. Which best depicts the response to L.S. that would use the process of "reflective listening"?
    A. Describe how you feel when you don't feel very good.
    B. You are having some issues with warfarin, yet you know it is important.
    C. It sounds like you are missing some doses, right?
    D. What can you do to help you not forget to take a dose?

7. L.S. shows the pharmacist a booklet on proper warfarin administration she was given upon hospital discharge but says she is having difficulty understanding the nonpharmacologic concepts described in the book. On further assessment, it is determined this patient grew up in the United States, dropped out of high school, and is not currently living in low-income housing, nor is she worried about housing stability. Which is most likely a risk factor for low health literacy in L.S.?
    A. Educational level.
    B. Race/ethnicity.
    C. Income level.
    D. Age.

D. Cultural Sensitivity
   1. Definitions (dbhds.virginia.gov/)
      a. *Cultural Knowledge* – Knowing about some cultural characteristics, history, values, beliefs, and behaviors of another ethnic or cultural group
      b. *Cultural Awareness* – Recognizing and understanding the cultural implications of behavior. *Consider* the impact of behaviors on others.
      c. *Cultural Sensitivity* – Integrating cultural knowledge and awareness into individual and institutional behavior. *Respond* to attitudes, feelings, and circumstances.
      d. *Cultural Competence* – Applying culturally appropriate health care interventions and practices regularly. *Accommodate* cultural differences in health care.
   2. Building cultural awareness. Health beliefs and behaviors affect participation in care and adherence to medications and other treatments.
      a. Build cultural awareness with patients by asking them questions and identifying their underlying values. It can be important to find and use appropriate resources to perform these tasks with diverse patient populations. EthnoMed was originally developed as a tool for clinicians and health care providers to increase awareness while working with immigrant populations. The website provides information about "immigration, cultural norms and values, experience with Western medicine, culture-specific information and tools pertinent to the clinical encounter, and translated/culturally tailored information for patients" (https://ethnomed.org/).
      b. The Health Belief Model uses four constructs (perceived susceptibility, severity, benefits, and barriers) to predict whether a patient will participate in disease prevention or treatment. By identifying an individual's disease-specific beliefs, providers can help identify barriers to adherence and create individualized educational messages.

Table 13. Using the Health Belief Model to Identify Issues and Tailor Educational Messages

Construct	Description	Patient Case Example	Tailored Educational Message
Perceived susceptibility	Individuals' beliefs about their likelihood of contracting the disease or condition	73-year-old woman continues to ask her provider for antibiotics to treat common colds and headaches. She states, "Anytime I get sick, a short course of antibiotics does the trick. There really isn't any downside!"	Explaining how the continued use of antibiotics can cause significant adverse effects (e.g., kidney disease, *Clostridioides difficile* infections) and can lead to resistant bacteria, which may affect her loved ones if they become infected
Perceived severity	Concern regarding the seriousness of the condition	43-year-old woman states, "I have had high blood pressure most of my adult life and I am still here. I feel just fine"	Explaining how the effects of high blood pressure can accumulate and present as additional complications (e.g., stroke, heart disease, kidney disease) later in life, but can be prevented by controlling blood pressure to goal according to evidence
Perceived benefits	Belief that making a suggested change can have an important impact	57-year-old man does not want to explore the benefits of a colonoscopy because "everyone I know who's had colon cancer has died. I'd just rather not know if I had colon cancer and die happy"	Explaining how getting a colonoscopy can help detect colon cancer in the earliest stages to allow more effective treatment and prevent the progression to advanced stages might help motivate this patient to seek out imaging

Table 13. Using the Health Belief Model to Identify Issues and Tailor Educational Messages *(cont'd)*

Construct	Description	Patient Case Example	Tailored Educational Message
Perceived barriers	Beliefs about the negative aspects of change	20-year-old man is recently diagnosed with celiac disease, but states, "I can't afford all these gluten-free foods. This is going to be impossible for me"	Explaining the benefits of eating gluten-free foods and discussing how many foods are naturally "gluten-free" (e.g., fruits, vegetables, and other whole grains); then, identifying local resources to use to obtain foods more economically
Cues to action	Factors that trigger action	82-year-old woman is unwilling to take prescription medications for depression but instead takes several supplements, including St. John's wort. She states, "My doctor thinks my constipation and dry mouth are from my supplements, but at least my depression is getting better!"	Explaining how the patient's supplements (especially St. John's wort) are not completely free of adverse effects and are most likely causing her current adverse effects. Also, discussing potential drug-drug interactions with her supplements and reviewing her current medication list to identify any potential issues
Self-efficacy	Confidence that one can perform the behavior to reach the desired outcome	65-year-old states, "At this point, I just can't see myself giving up smoking. It was impossible for me to build up the willpower on my own"	Explaining the improved rates of complete smoking cessation with the addition of pharmacology (varenicline, bupropion, or nicotine replacement) and with the support of several health care professionals

3. Developing cultural sensitivity
    a. Identify implicit biases to navigate personal thoughts and feelings within the Health Care Model.
        i. Unconscious (or implicit) bias occurs when this automatic processing is influenced by stereotypes; therefore, these stereotypes affect actions and judgments
        ii. Take personal inventories of implicit biases for increased self-awareness (https://implicit.harvard.edu/).
4. Fostering cultural competency: The "**ETHNIC**" model is a framework for culturally competent clinical practice. By considering each of the factors within this model, practitioners can improve their overall cultural sensitivity in patient-care situations to place the patient at the center of care.
    a. Explanation. It is important to remember illness and disease are two distinct entities, so asking patients or providers to explain their understanding of the issue in their own words can be helpful to better understand the situation. ("Why do you think you are having this symptom?")
    b. Treatment. Discovering what treatments have already been pursued can be helpful in knowing what alternatives the patient or provider believes to be effective, safe, or acceptable. ("What have you tried to help with this problem?" – medications, home remedies, traditional therapies, etc.)
    c. Healers. It is important to realize that patients from various cultures may seek out help and advice from other voices and not exclusively look to "Western" medicine. ("Have you sought help from anyone for this problem?" – friends, physicians, folk healers, etc.)
    d. Negotiate. Discussing mutually acceptable options that incorporate the patient's beliefs continue to put patients at the center of their own care. ("We've talked about a number of options. Which of these options do you feel most comfortable pursuing?").
    e. Intervention. After building rapport and trust, a patient or provider can decide on a specific intervention which may include incorporating alternative treatments, spirituality, and healers as well as other cultural practices. ("In addition to starting this new medication, what are your thoughts on seeking counsel or mentorship from those within your faith community?")

f. Collaboration. Including important people in the decision-making process such as family members, other health care team members, healers, and community resources may be considered acceptable and even an important part of different cultures. ("Who else would you feel comfortable sharing your plan for solving this problem with?").

E. Assessing Effectiveness of Patient Education and Adherence to Plan
   1. Assessing patient adherence
      a. *Compliance*: Degree to which a patient's behavior is consistent with the prescriber's recommendation
      b. *Adherence*: Degree to which a patient's behavior meets the agreed plan for the prescriber. This is the generally accepted term in the literature in the United States.
         i. *Persistence*: Whether the patient continues a medication beyond the first refill. In general, taking 80% or more of the prescribed doses is considered "acceptable" adherence; however, this may vary depending on the prescription medication (e.g., insulin).
         ii. Primary nonadherence: Patient never fills or fills but does not initiate the medication or behavior change
         iii. Secondary nonadherence: Patient begins but subsequently discontinues a medication or behavior change
         iv. Improper use: Patient continues to take the medication but in a manner inconsistent with the prescriber instructions (e.g., different dose, frequency, or duration)
      c. Measuring adherence
         i. Adherence can be indirectly calculated using proportion of days covered or the medication possession ratio from prescription refill history at the pharmacy or while using information from the insurance claims history (http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf).
         ii. Direct measurements such as pill counts, finishing pill packets, and other methods can be performed but have several limitations. These can be time- and labor-intensive and cannot determine the reason for nonadherence. For example, a patient may have a higher pill count than expected but may have forgotten to take the medication or may be taking the incorrect dosing, or a patient may be taking a tablet once daily when they are supposed to be taking the tablet twice daily).
      d. Predicting future nonadherence
         i. The "Adherence Estimator" is a prospective assessment of the likelihood that a patient will adhere to a newly prescribed medication (e.g., the likelihood a patient with a new prescription for a statin medication will continue to take the medication after the first fill) (Curr Med Res Opin 2009;25:215-38).
            (a) Purpose: The estimator is simple and easy to administer and score; however, it assesses the risk of nonadherence to a single drug regimen, not the entirety of a patient's medications (e.g., potential nonadherence is assessed for metformin given to a patient, but current use of other medications the patient may be taking is not assessed).
            (b) Questions: Patients are asked a series of three questions to measure their perception of the new medication, but questions do not assess the medication's toxicity, efficacy, or cost. (Three questions are included: "I am convinced of the importance of my prescription medicine." "I worry that my prescription medicine will do more harm than good to me." "I feel financially burdened by my out-of-pocket expenses for my prescription medicine.")
            (c) Scoring: Each question is scored on a 6-point scale from agree completely to disagree completely, and depending on responses, points are totaled to fall within low, medium, and high risks of nonadherence (https://www.ehidc.org/sites/default/files/resources/files/Adherence%20Estimator%20Kit_%20Interactive%20PDF.pdf).

ii. The Morisky questionnaire is another prospective assessment tool used to measure adherence (J Clin Hypertens 2008;10:348-54).
   (a) Purpose: Useful in identifying and screening for knowledge gaps and motivational issues affecting adherence. Focuses on the entirety of disease-specific drug regimens (e.g., diabetes, hypertension) and predicts the likelihood of adhering to multiple medications.
   (b) Questions: Available in four- and eight-question formats with questions asking about missed doses, stopping medications, or cutting back on a medication because of adverse effects or disease control (e.g., "Do you sometimes forget to take your diabetes pills?" "Over the past 2 weeks, were there any days when you did not take your diabetes medicine?")
   (c) Available in English, French, Chinese, and other languages. These forms are available for a fee, depending on the level of questionnaire desired (e.g., the four- or eight-question scale) (www.moriskyscale.com/).

2. Delivering patient counseling for drug information
   a. "Universal precautions" approach widely recommended
      i. Regardless of health literacy, patients may have difficulty with medication concepts because of topic-specific misconceptions or gaps in knowledge or skills. Only 12% of the U.S. adult population has the health literacy skills needed to meet the demands of navigating the health care system.
      ii. Specific tools aimed at improving verbal and written communication, self-management, empowerment, and supportive systems can be accessed through the Health Literacy Universal Precautions Toolkit at https://www.ahrq.gov/health-literacy/improve/precautions/index.html.
   b. "Elicit-provide-elicit" method (https://motivationalinterviewing.org/category/resource-tag/elicit-provide-elicit)
      i. Elicit what the patient knows or would like to know or whether it is OK if you offer them information.
         (a) Ask open-ended questions to obtain baseline information important to the patient: "What do you know about the shingles vaccine?"
         (b) Use the Indian Health Service three prime questions to assess the patient's baseline knowledge regarding a specific medication.
            (1) "What did your prescriber tell you the medication was for?"
            (2) "How did your prescriber tell you to take the medication?"
            (3) "What did your prescriber tell you to expect?"
      ii. Provide information in a neutral, nonjudgmental fashion.
         (a) Ask for permission for providing input. "Do you mind if I share a little information on the vaccine?" "Would it be OK if I give you some stats about the vaccine's success rates?"
         (b) Ensure information given remains as objective as possible and is focused on the patient's core concerns.
      iii. Elicit the patient's interpretation of the new information: "What do you think after hearing those points?" "Where does this leave you with getting the shot?"
      iv. General tips for effective use of the elicit-provide-elicit model
         (a) Use neutral language as much as possible. "What we know is…" "Some people have found…" "Others have benefited from…"
         (b) Use conditional words (e.g., "might," "perhaps," "consider") instead of concrete words (e.g., "should," "must").
         (c) Avoid sentences starting with "I" or "You" and focus on the team effort. "We can circle back to this if possible, the next time we see each other."

c. Focus the conversation on key points and what the patient wants to gain from the interaction. A practice called "agenda mapping" can be done in creative ways such as using a visual cue (e.g., easel paper pad, brainstorming web) or other documentation to keep track of a specific topic of interest between visits. For example, a patient with diabetes may be given the choice between "medications", "movement", "meal planning", "monitoring", or "mental" and the use of labels with these terms can help a patient stay on track to the area of focus at any specific time. "What do you want to focus on the most during this conversation?"

d. "Teach-back" and "show-me" methods
   i. These methods are valuable for everyone to use with each patient. They can help improve patient understanding and adherence, decrease callbacks and canceled appointments, and improve patient satisfaction and outcomes (www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/healthlittoolkit2_tool5.pdf).
      (a) Keep in mind this is not a test of the patient's knowledge, but instead a test of how well the concept was explained.
      (b) Plan the approach. "We covered a lot of information today. I want to make sure I explained myself clearly, so I'd like for you to tell me how you are going to make the change to your insulin dosing."
      (c) "Chunk and check." Use the teach-back method throughout the interaction with the patient, without waiting until the end to repeat all the information.
      (d) Clarify and check again. If a mistake is uncovered using this method, ask the patient to use repeat-back until they can correctly describe it in their own words. "I want to make sure you are able to get this, so can you repeat that again?"
      (e) Start slowly and use consistently. Use this method with patients who are familiar at first, and then work this concept into all patient interactions.
      (f) Practice. Mastery of this concept takes time and individual customization. This can be implemented efficiently if given the time for practice.
      (g) Use the "show-me" method when dispensing/prescribing new medicines or changing a dose. "Giving a child the correct dose of liquid medication can be challenging. Can you please show me how you plan to give your child their antibiotics?"

e. Use handouts (if applicable) together with teach-back. Collect and disseminate published resources for given disease states. "We have a variety of resources to help you count your carbohydrates while giving the correct insulin doses. Would it be helpful if gave you some of these booklets?"

f. Use clear communication ("plain language") when using handouts and other forms of written communication to provide effective education to the audience for first-time understanding (https://www.cdc.gov/healthliteracy/pdf/checklist-H.pdf).
   i. Organize to serve the audience.
      (a) Know the audience and purpose before beginning.
      (b) Put the most important message first.
      (c) Present other information in order of importance to the audience.
      (d) Break text into logical chunks and use headings.
   ii. Choose words carefully.
      (a) Write in the active voice: "Take 2 tablets for the next 2 weeks."
      (b) Choose words and numbers the audience knows: "Check your blood sugar using the meter and call the pharmacy team if the number is less than 70."
      (c) Keep sentences and paragraphs short.
      (d) Include "you" and other pronouns.
   iii. Make information easy to find.
      (a) Use headings and text boxes.
      (b) Delete unnecessary words, sentences, and paragraphs.
      (c) Create lists and tables (e.g., create a list of medications that might interact with warfarin).

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
From an off-label use perspective, many tertiary resources could provide helpful information. In this case the correct answer is AHFS Drug Information, which provides fairly detailed overviews of a fair number of potential off-label uses (Answer A is correct). The manufacturer-provided prescribing information would not provide this information since it must be approved by FDA (Answer D is incorrect). DailyMed and Drugs@FDA only provide FDA-approved information and would not cover off-label uses (Answers B and C are incorrect).

2. Answer: D
A grade of III suggests either no benefit or harm according to the AHA grading scheme (Answers B and C are incorrect). In this case, the medication is stated to be grade III, no benefit, suggesting it is not recommended but is also not harmful (Answer A is incorrect). A level of evidence of B-NR could be several article types, including observational or nonrandomized trials (Answer D is correct).

3. Answer: D
Because the groups are formed on the basis of an exposure (i.e., IVIG or no IVIG) likely to influence an outcome (i.e., survival or no survival) and because the study was defined as observational (there was no randomization or other formal group assignment), this would be considered a cohort study (Answer D is correct). It is retrospective/historical because it is based on past rather than current exposures. It is not a case-control study because the groups were not formed on the basis of an outcome (Answer A is incorrect). It is not an interrupted time series or noncontrolled trial because it is observational rather than experimental (Answers B and C are incorrect). It is also not considered a noncontrolled trial because two groups are being compared.

4. Answer: A
The most relevant terms in the case are acute myocarditis (P, patient/problem), IVIG (I, intervention), and inpatient (S, setting). No clear C (comparator/control) or O (outcomes) terms are posed by the specific clinical question. The answer that correctly pairs the PICOS type with the term is P, since acute myocarditis is the primary problem of interest (Answer A is correct). The other three terms are relevant but mispaired; pediatric would be a secondary P term (Answer B is incorrect), IVIG is the main drug of interest, the I term (Answer C is incorrect), and hospitalization/inpatient represents the setting of the question or S term (Answer D is incorrect).

5. Answer: D
Using the regular PubMed interface with automatic term mapping would not only search using MeSH terms, but also the keywords in the "all fields" search, which theoretically should make the search more sensitive and not reliant on correct indexing (Answer D is correct). Using MeSH terms only may limit results by removing the "all fields" search (Answer C is incorrect). Filtering results will yield a more specific set of articles (Answer A is incorrect) and adding terms using "OR" will expand results (Answer B is incorrect).

6. Answer: B
Reflective listening is the process of rephrasing the key points discussed (Answer B is correct). This statement uses "creating ambivalence" because it not only helps validate the patient's concerns about warfarin, but also helps the patient see their own self-stated need for the medication. This statement will likely help the patient see their dilemma and further expand on both of these points. Answer A is a good example of the "show-me" method and can help identify the patient's reasons for nonadherence. Answer C is an example of a leading question and should be avoided. Answer D might eventually help provide the patient with a plan for improved adherence moving forward.

7. Answer: A
This patient's educational level is the most likely risk factor for low health literacy, given that she has not completed high school (Answer A is correct). Each distractor is incorrect because this patient's income is not classified as "low" (Answer C is incorrect), and patients 65 and older are generally accepted to have an increased risk of low health literacy (Answer D is incorrect). It should also not be assumed that because the patient is of Hispanic background, English is her second language (Answer B is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

In the abstract, the authors discuss that the article was a comprehensive review prepared using PubMed, Embase, and other secondary resources. Review articles are considered tertiary resources because they synthesize information from several primary literature sources and do not present original research results, even though they are published as journal articles (Answer C is correct; Answers A is incorrect). The article is not a secondary source because this type of literature consists of indexing and abstracting services (Answer B is incorrect). There is not a category of "quaternary" literature under this scheme (Answer D is incorrect).

2. Answer: C

Because the study involves comparing outcomes for patients who received treatment under a new, practice-based initiative with outcomes for similar patients who were not involved in the initiative, it is most like the interrupted time series or a historical control (Answer C is correct). If patients who experienced an outcome (e.g., heart failure hospitalization) were compared with similar patients who did not, the study would more resemble a case-control study (Answer A is incorrect). A cluster RCT or non-equivalent control group would involve randomizing patients to treatment with the new protocol or an older protocol on the basis of an external factor, like their provider or hospital unit (Answer B is incorrect). A noncontrolled trial would involve analysis of a single group of patients who received treatment under the new protocol (Answer D is incorrect).

3. Answer: D

The best PICOS question is hypertension/aortic dissection, lisinopril twice daily, lisinopril once daily, blood pressure, and outpatient/community. The most appropriate "I" (intervention) term is lisinopril twice daily because it includes the specific drug of interest and represents the departure from "usual care" (Answers A, B, and C are incorrect). The most appropriate "C" (comparator) term is thus lisinopril once daily (Answer D is correct). Hypertension and aortic dissection are both relevant "P" (patient) terms because they are specific to the requested use, though hypertension may be more critical to include as a formal search term. Blood pressure is the most relevant "O" (outcome) term because quality of life was not a focus of the question compared with surrogate outcomes. The setting ("S" term) is outpatient or community.

4. Answer: A

One of the most important background questions related to adverse effects inquiries is to determine whether the question is theoretical or whether the person suspects an adverse effect occurred. Asking this in an open-ended way can help the pharmacist learn much more about the patient's recent experiences (Answer A is correct). It may also be good to figure out why the patient is taking the drug, but this is not as high priority at the moment and possibly could also be verified electronically (Answer D is incorrect). Because it is already clear that the patient has obesity, the patient's exact weight is not needed at this time for this inquiry (Answer B is incorrect). It would likely be relevant to obtain the full list of medications and supplements to determine whether an interaction is occurring, but it is higher priority to learn about the adverse event of interest first (Answer C is incorrect).

5. Answer: A

Because there are more than 25 but less than 100 results, activating a filter is likely the best strategy. Using the clinical studies filter will remove commentaries, reviews, and other articles and help focus the search on the types of articles described in the question (Answer A is correct). Adding a MeSH term for major bleeding is the second-best choice, but at this point, adding a "fourth" term might cause the search to be overly specific (Answer C is incorrect). Combining drug class terms with OR and changing to a non-MeSH approach would likely increase the number of results (Answers B and D are incorrect).

6. Answer: B

Proxemics focuses on the physical distance between people and thus is being used in the decision-making process in this scenario (Answer B is correct). Haptics involves the use of touch, kinesis involves the use of body movements, and chromatics involves the use of time (Answers A, C, and D are incorrect).

7. Answer: A
A low-priority message sent within the electronic health record would be appropriate; this case does not require urgent attention because the provider does not need an answer within the next few weeks (Answer A is correct; Answer B is incorrect). A direct page to the physician with the results would be inappropriate unless additional information is necessary (Answer C is incorrect), and a call to the physician's nurse would not be required because this information can be communicated directly with the physician (Answer D is incorrect).

8. Answer: A
This patient is having difficulty with the most basic levels of mathematical calculations and inferences, even with the simplest dosing schedule, so the patient would fall under the "below basic (level 1)" health literacy level (Answer A is correct). The difference between basic and below basic would be the ability to do the most basic calculations and inferences, which this patient cannot do (Answer B is incorrect). Nor is the patient at the intermediate or proficient levels, given the scenario (Answers C and D are incorrect).

9. Answer: D
The s-TOFHLA would fit each of the criteria in this scenario because it can be administered in 7 minutes, is available in both Spanish and English, and can assess both literacy and numeracy (Answer D is correct). The REALM-SF would be helpful but is not readily available in Spanish (Answer A is incorrect). The SAHLSA-50 is intended only for Spanish-speaking patients; thus, English-speaking patients would not be represented (Answer B is incorrect). The SILS assessment, though administered quickly, would not be available for Spanish-speaking patients and does not assess numeracy (Answer C is incorrect).

10. Answer: C
Cultural sensitivity requires individuals to assess their personal implicit biases and increase their own self-awareness in order to appropriately respond to others' attitudes, feelings, and circumstances (Answer C is correct). A book club might help increase cultural sensitivity, but it would likely mainly promote cultural knowledge (Answer A is incorrect). EthnoMed resources help with cultural awareness within specific patient populations (Answer B is incorrect). The ETHNIC model is the culmination of cultural competence and may not be effective until cultural sensitivity is increased (Answer D is incorrect).

11. Answer: C
The Morisky questionnaire is effective at assessing adherence to complex drug regimens and identifying patients' thoughts about their medications (Answer C is correct). The Adherence Estimator is mainly used to determine future adherence to one specific drug regimen, but in this case, the antihypertensive regimens may include more than one agent (Answer B is incorrect). The PEMAT is useful in creating educational materials for patients (Answer A is incorrect), and the NVS is for assessing health literacy (Answer D is incorrect).

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